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BACTERIOLOGIC OBSERVATIONS ON ACUTE TONSILLITIS WITH REFERENCE TO EPIDEMIOLOGY AND SUSCEPTIBILITY *

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Despite the great amount of information that has been assembled on the nature of infectious disease, many fundamental problems remain unsolved. Among others, the question of just how existing balances between micro-organism and host are upset so as to lead to the spread of infection in epidemic form, demands explanation. It is clear, for example, that all cases of lobar pneumonia may be traced back ultimately to a previous case or to a pneumococcus carrier, but just how and why such a carrier will give rise to disease at one time and be harmless at another, is quite obscure. Similar considerations apply to other infections.

The lack of exact information on this question may be due in a measure to the mode of attack which has been employed; when clinical epidemiologic studies have been adequate, exact bacteriologic control has usually not been available, and, vice versa, exact bacteriologic studies have usually been conducted under conditions inadequate to give the desired epidemiologic facts. It has become apparent to students of infectious disease that the mere accumulation of masses of statistics by health boards and insurance companies, while of inestimable value, fails to explain the intimate and essential details of the spread of bacterial infection. Attempts have been made recently by several men to attack the problem by means of experimental epidemics in animals [1] which can be controlled both from the bacteriologic and biometric standpoint, and facts of great importance and interest have been brought out;

* From the Biological Division of the Medical Clinic, Johns Hopkins University and Hospital.

* This is the second of a series of papers on streptococcus infection with special reference to acute tonsillitis.

1. Amoss, H. L.: J. Exper. Med. **26**:25 (July) 1922. Topley, W. W. C.: J. Hygiene **19**:350, 1920-1921.

however, the conditions of these experiments are so highly specialized that a certain amount of reservation must be exercised in transferring the conclusions to human infection.

It seemed that if an outbreak of disease among people could be studied with an accuracy and rigidity of control approximating that attainable in an experimental epidemic, valuable information might be obtained. Such an opportunity was available in the case of a limited group of people among whom there is each winter a high incidence of acute streptococcic tonsillitis. This article concerns itself with a study of this group with the purpose, not only of obtaining exact information about the cause and epidemiology of tonsillitis, but also of deducing if possible general conclusions about the mode of spread of bacterial infection.

The group which was studied comprised approximately 200 young women—members of the training school for nurses of the Johns Hopkins Hospital. Although segregated and readily available for controlled study, conditions as regards crowding and general environment were in no way different from those which obtain in the city at large. These students are housed in several commodious buildings, not more than two live in one room, and there is free communication between the whole group and the outside world. The only occasions when more or less general contact may exist are in the dining room, in class and at the daily assembly. The general hygienic conditions are excellent.

Through the cooperation of the supervisors of nurses, it was possible to obtain cultures at any time from the members of the group, to keep accurate records of the occurrence of tonsillitis and other infections and to follow contacts.

It was assumed from our own experience as well as from observations in the literature that acute tonsillitis is usually an infection caused by hemolytic streptococci of the beta type. This supposition was confirmed by the later work, as will be pointed out. The plan of study was briefly as follows:

1. A detailed survey of the experimental group for hemolytic streptococci at a time when no acute streptococci disease was present.

2. A bacteriologic study of such cases of tonsillitis as might later occur in the group in order to determine whether (*a*) tonsillitis is an autogenous infection by a strain of streptococcus previously carried by the person, and if so, the factors which lead to a seasonal outbreak, or whether (*b*) tonsillitis is an exogenous infection due to some outside strain or strains.

3. The relation of carriers and of contacts to the spread of tonsillitis in the group.

4. The relation of season, weather, other infections, etc., to the outbreak of tonsillitis.

5. General epidemiologic observations with a view to defining epidemic and sporadic disease.

The present report deals with the bacteriology, and epidemiologic definition of acute tonsillitis.

BACTERIOLOGIC OBSERVATIONS ON ACUTE TONSILLITIS

In a previous paper,[2] we presented the results of a survey of this experimental group of people for the presence of beta hemolytic streptococcus at a time when streptococcus disease was not prevalent. These observations, made in September and October, 1922, served as a base line with which to compare the findings in disease presented below. In brief, there were 175 controls. Of sixty-seven whose tonsils had been removed, 9 per cent. showed a few scattered colonies of beta hemolytic streptococcus in the throat, whereas of 108 whose tonsils had not been removed, 37 per cent. yielded the organisms, usually in large numbers, from the tonsil crypts.

In the early part of October, tonsillitis began to occur in the group, and from that time until April 1, 1923, when the experiment was concluded, there were in all thirty-nine cases.[2] Their distribution in relation to epidemiologic considerations will be discussed later, but it may be said now that no significant contact could be demonstrated between successive cases. All of the patients were under close observation during the attack, for the most part in the wards, and they were followed throughout the remainder of the season.

The method of study was essentially similar to that previously described in connection with the control observations[3] except that it did not seem advisable to probe the tonsil crypts during the acute stage of the tonsillitis. Three cultures were taken from each patient by rubbing cotton swabs over: (1) the posterior pharyngeal wall, (2) the right tonsil, and (3) the left tonsil. These swabs were diluted in broth from which blood-agar plates were poured. In studying the cultures, notes were made of the predominating type of bacteria, with especial reference to beta hemolytic streptococcus, the relative and absolute numbers obtained in each culture, and the apparent identity of the various colonies of streptococci on the same plate. Several colonies were fished from each plate and preserved for study. The results of the cultures are summarized in Table 1, the first item in each case representing the culture made during the acute stage of the disease.

It was found, in the first place, that hemolytic streptococci are invariably predominant in the cultures made during the active stage of the disease. Furthermore, if cultures from the pharynx and from the

2. The clinical features of these cases are discussed in another paper.
3 Bloomfield, A. L., and Felty, A. R.: Arch. Int. Med.

TABLE 1.—*Occurence of Beta Hemolytic Streptococci in Cases of Tonsillitis During the Disease and Later*

Case	Date	Days After Onset of Disease	No. of Beta Hemolytic Streptococci Recovered from			Remarks
			Pharynx	Right Tonsil	Left Tonsil	
1	9/ 3/22	4	∞	∞	∞	
	9/ 8/22	9	1% of plate	Many	∞	Patient ambulatory
	1/30/23	154	2 colonies	∞*	∞*	
2	10/ 6/22	2	1 colony	∞	∞	
4	10/ 6/22	2	∞	∞	∞	
5	10/ 6/22	2	20 colonies	∞	∞	
	1/26/23	112	10% of plate	5% of plate	5% of plate	Patient ambulatory
6	10/ 7/22	2	50% of plate	∞	∞	
7	10/ 9/22	2	Many	∞	∞	
	10/18/22	11	30% of plate	∞	∞	Patient ambulatory
	1/23/23	109	None	20 colonies*	None*	
8	10/ 9/22	2	Many	∞	∞	
	10/16/22	9	Many	∞	∞	Patient ambulatory
	1/24/23	110	None	None*	1 colony*	
	1/26/23	112	None	None*	None*	
9	10/18/22	2	10% of plate	∞	∞	
	1/23/23	97	None	Many	None	Patient ambulatory
10	10/17/22	2	None	∞	∞	
	1/24/23	90	None	∞*	2 colonies*	Patient ambulatory
11	10/30/22	4	Many	∞	∞	
12	11/13/22	2	∞	∞	∞	
	1/24/23	78	None	Many*	Few*	Patient ambulatory
13	10/19/22	2	Many	Many	Many	
	1/23/23	64	None	2 colonies*	None*	Patient ambulatory
14	11/23/22	2	None	∞	∞	
	1/23/23	61	None	None*	None*	Patient ambulatory
15	11/23/22	2	∞	∞	∞	
	1/23/23	61	1 colony	∞*	½ of plate	Patient ambulatory
16	11/25/22	2	∞	∞	∞	
17	12/ 2/22	2	25% of plate	∞	∞	
	1/30/23	61	None	6 colonies*	None*	Patient ambulatory
18	12/ 6/22	2	∞	∞	∞	
19	12/ 9/22	2	Many	∞	∞	
	1/23/23	55	1 colony	50% of plate*	∞*	Patient ambulatory
20	1/ 4/23	3	∞	∞	∞	
21	1/ 5/23	2	—	∞	∞	
22	1/ 6/23	2	∞	∞	∞	
23	1/ 6/23	2	∞	∞†	∞†	Tonsillectomy 11/'21
	3/20/23	73	None	None†	None†	Patient ambulatory
24	1/ 6/23	2	∞	∞	∞	
25	1/12/23	2	∞	50% of plate†	—	Tonsillectomy 14 years ago
	1/23/23	13	Few	50% of plate†	30% of plate†	Patient ambulatory
	3/20/23	67	None	2 colonies†	None†	
26	1/19/23	2	∞	∞	∞	
27	1/22/23	3	∞	∞	∞	
	1/23/23	4	∞	∞	∞	
	1/24/23	5	∞	∞	∞	
28	1/24/23	3	Many	∞	∞	
29	1/25/23	2	—	∞	∞	
30	1/21/23	1	∞	∞†	∞†	Tonsillectomy 8 yrs. ago
31	1/29/23	2	∞	∞	∞	
32	2/19/23	2	∞	∞	∞	
33	2/19/23	2	50% of plate	50% of plate	50% of plate	Picture not as outspoken as usual
34	2/26/23	4	None	Many	Many	
35	2/26/23	2	∞	∞†	∞†	Tonsillectomy 6 yrs. ago
	3/20/23	24	None	None†	None†	Patient ambulatory
36	2/26/23	2	∞	∞†	∞†	Tonsillectomy in March 1921
	3/20/23	24	None	5% of plate†	5% of plate†	Patient ambulatory
37	2/27/23	2	∞	∞	∞	
38	3/ 2/23	2	∞	∞†	∞†	Tonsillectomy 1 year ago
39	3/ 4/23	2	∞	∞	∞	
40	3/ 9/23	2	∞	∞	∞	

∞ indicates innumerable and almost pure culture, *, crypt culture; †, culture from tonsil fossa.

tonsils are compared, it is seen that the latter in practically every case yielded the bacteria in pure or almost pure culture and in tremendous numbers, whereas the pharyngeal cultures were less regular and as a rule showed many less hemolytic streptococci. This seems to indicate that the infection is primarily tonsillar, with an overflow of bacteria to the surrounding mucous membranes. Apart from the tonsil, the degree of infection seems to depend on the extent of development of lymphadenoid tissue in the throat. This is brought out by a group of six cases (Nos. 23, 25, 30, 35, 36 and 38) occurring in people whose tonsils had been removed. Under these conditions the disease affected bits of lymphoid tissue which remained in the tonsillar fossae and the small nodules present behind the posterior pillars and sometimes on the posterior pharyngeal wall.

The hemolytic streptococci obtained were in every case typical of the beta group, as defined by Smith and Brown.[4] There was a wide (1 to 2 mm.) and total zone of hemolysis about the colony without any greenish or yellowish discoloration. Furthermore, all the colonies in any one case appeared identical and whenever several were tested they gave identical reactions, although they varied somewhat in appearance in different cases. The biologic classification of the strains will be taken up in detail in another paper.

Two further points should be stressed. First, the number of hemolytic streptococci recovered bore no relationship to the severity of the clinical infection. In several cases which were mild, and which showed only slight redness and enlargement of the tonsils with swelling of the follicles and a transient rise in temperature of one or two degrees, the cultures yielded hemolytic streptococci almost pure, just as in the severe cases. In the second place, in no culture from a condition which could not be diagnosed clinically as a definite tonsillitis were real beta hemolytic streptococci recovered. It appears, therefore, that upper respiratory tract infections, especially certain types of pharyngitis, which are sometimes loosely spoken of as streptococcus throats, are not caused by real beta hemolytic streptococci, but that organism confines its activity to clinically recognizable infections of the lymphadenoid tissue, especially in the vicinity of the tonsils. Furthermore, a culture showing no beta hemolytic streptococci, if properly made, would be strong evidence against acute follicular tonsillitis and in favor of some other infection such as diphtheria or Vincent's Angina.

In a previous paper,[3] it was suggested that focal carriage of beta hemolytic streptococcus in the tonsil might date from a previous acute tonsillitis. This opinion was based on cultural studies of healthy controls together with their histories. It seemed of interest to check this

4. Brown, J. H.: Monograph No. 9, Rockefeller Institute, 1919.

point further by studying convalescents for the persistence of beta hemolytic streptococcus. Brown,[4] working with surface throat cultures, found that early in convalescence from acute tonsillitis the real beta hemolytic types of streptococcus began to disappear and were replaced by alpha prime, alpha and green producing types. A truer idea of persistence can, however, be obtained by cultures of aspirated crypt material. Such a method applied in the present series showed that real beta hemolytic streptococcus persisted in the tonsils for long periods of time, although the pharynx cultures yielded only a few or none of the organisms. A transition took place from conditions found in the acute infection to a focal tonsillar carriage. On the other hand, in the six cases of acute streptococcus lymphadenoid infection in subjects whose tonsils had been removed, the organisms diminished and disappeared with relative rapidity. The exact biologic relationship of streptococci recovered after various intervals from convalescents to the disease strain will be discussed in detail later, but it may be said now that a strain recovered as late as 154 days was identical with the original culture made during the acute attack.

The details of the recultures are given in Table 1 and are summarized in Table 2. Of fifty-three cultures in nontonsillectomized cases made up to the one hundred and fifty-fourth day, only one was negative (on the one hundred and twelfth day), whereas of eleven cultures made in tonsillectomized cases up to the seventy-third day, two had become negative (seventy-third day, twenty-fourth day), and one showed only two colonies (sixty-seventh day). It appears, then, that real beta hemolytic streptococci may persist in the tonsil for an indefinite length of time after acute tonsillitis, but dies out rapidly on the free mucous membranes of the throat.

RELATION OF OCCURRENCE OF TONSILLITIS TO PREVIOUS CARRIER STATES

One of the main objects of the present study was to determine whether acute tonsillitis is usually an autogenous infection from a strain already carried in the tonsils or whether it represents invasion by a fresh outside strain. Control cultures had been made in the experimental group. When cases of tonsillitis later began to appear it soon was obvious that the infection occurred in those who previously had not been carriers of beta hemolytic streptococcus, whereas the carriers with one exception failed to develop acute tonsillitis. These facts are summarized in Table 3. It appears that of thirty-four people who developed tonsillitis, only one was previously a carrier of the beta hemolytic streptococcus. The interval between negative control culture and onset

TABLE 2.—*Duration of Persistence of Beta Hemolytic Streptococcus in Tonsil Crypts Following Acute Tonsillitis*

Days After Onset of Acute Infection That Culture Was Made	No. of Cases	Beta Hemolytic Streptococcus		Remarks
		Present	Absent	
Nontonsillectomized Cases				
125–154	1	1	0	
100–125	4	3	1	
75–100	3	3	0	
50– 75	5	5	0	
0– 50	40	40	0	
Tonsillectomized Cases				
73	1	0	1	
67	1	1	0	Only 2 colonies recovered
24	2	1	1	
13	1	1	0	
0-5	6	6	0	

TABLE 3.—*Relation of Occurence of Acute Streptococcic Tonsillitis to Previous Streptococcus Carrier State*

Case	Control Culture for Hemolytic Stretptococcus		Culture During Acute Tonsillitis		Days Between Control Culture and Onset of Tonsillitis
	Date	Result	Date	Result	
1	Not made	.....	8/30/22	Positive	
3	Not made	.....	10/ 6/22	Positive	
4	9/25/22	Negative	10/ 6/22	Positive	11
5	9/30/22	Negative	10/ 6/22	Positive	6
6	Not made	.....	10/ 7/22	Positive	
7	Not made	.....	10/ 9/22	Positive	
8	Not made	.....	10/ 9/22	Positive	
9	9/12/22	Negative	9/18/22	Positive	36
10	9/ 7/22	Negative	10/17/22	Positive	40
11	9/23/22	Negative	10/29/22	Positive	36
12	10/20/22	Negative	11/11/22	Positive	22
13	9/ 1/22	Positive	11/14/22	Positive	74
14	10/16/22	Negative	11/23/22	Positive	38
15	10/18/22	Negative	11/23/22	Positive	36
16	10/10/22	Negative	11/25/22	Positive	46
17	9/17/22	Negative	12/ 2/22	Positive	76
18	10/20/22	Negative	12/ 6/22	Positive	47
19	10/16/22	Negative	12/ 9/22	Positive	54
20	10/12/22	Negative	1/ 4/23	Positive	84
21	9/29/22	Negative	1/ 5/23	Positive	98
22	9/ 7/22	Negative	1/ 5/23	Positive	110
23	10/10/22	Negative	1/ 6/23	Positive	88
24	9/30/22	Negative	1/ 6/23	Positive	98
25	10/18/22	Negative	1/12/23	Positive	86
26	9/21/22	Negative	1/19/23	Positive	120
27	9/ 7/22	Negative	1/12/23	Positive	127
28	10/26/22	Negative	1/22/23	Positive	98
29	9/12/22	Negative	1/25/23	Positive	145
30	10/10/22	Negative	1/29/23	Positive	111
31	10/20/22	Negative	1/29/23	Positive	101
32	9/25/22	Negative	2/19/23	Positive	147
33	10/16/22	Negative	2/21/23	Positive	128
34	10/ 9/22	Negative	2/23/23	Positive	137
35	10/ 5/22	Negative	2/24/23	Positive	142
36	9/15/22	Negative	2/26/23	Positive	164
37	10/ 9/22	Negative	2/27/23	Positive	141
38	10/ 5/22	Negative	3/ 2/23	Positive	148
39	9/15/22	Negative	3/ 4/23	Positive	170
40	10/26/22	Negative	3/ 9/23	Positive	170

of disease varied from five to 170 days. The briefer intervals are of interest in so far as they may indicate that the streptococcus is not carried for any length of time before disease occurs.

In summary, then, in the present series tonsillitis was distinctly not an autogenous infection but resulted from invasion by an outside strain. The strains concerned were not identical but, as will be shown later, fell into several groups.

It would be of great interest to determine the time of acquisition of the beta hemolytic streptococcus in relation to the onset of acute tonsillitis in a number of cases, but this could only be done by making frequent cultures in a susceptible group. By chance a single observation was made which may be mentioned. In Case 31 a control culture was made on Oct. 18, 1922, which yielded no beta hemolytic streptococci. On Jan. 31, 1923, this patient entered the ward with a typical attack of influenza. A throat culture now showed a few scattered colonies of

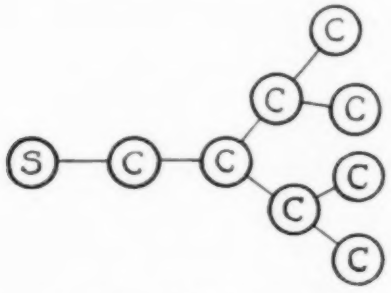


Fig. 1.—The essential features of an epidemic. In this and in the following illustrations, *S* represents source and *C* case or carrier.

the beta hemolytic streptococcus. There were no symptoms or evidence of tonsillitis. On the following day, she developed a mild but definite acute follicular tonsillitis. Culture now showed innumerable beta hemolytic streptococci in practically pure culture from both pharynx and tonsils. In this case at least, the advent of the organism preceded the onset of the disease.

EPIDEMIOLOGIC DATA

In the preceding sections, certain facts have been presented which may be briefly summarized:

1. Acute tonsillitis in the present group of cases was invariably an infection with beta hemolytic streptococci.

2. The disease affected almost uniformly a group of people who were not previously carriers of this organism.

3. Carriers, although equally exposed, did not develop acute tonsillitis, except in one case.

4. No special clinical or bacteriologic association could be demonstrated between successive cases of tonsillitis in the present group.

It remains, then, to attempt to place the present outbreak in a proper epidemiologic setting. Among the 175 members of the group there occurred, during six months, thirty-nine cases of tonsillitis—a rate of 22 per cent. A similar incidence of typhoid fever, scarlet fever or many other acute infectious diseases would stimulate more serious consideration than a mild disease such as tonsillitis, but the problem remair of no less interest from a purely epidemiologic standpoint. In brie , ...e point which it seemed desirable to settle was whether the present outbreak represented a true epidemic or merely a large group of sporadic cases.

If one considers the feature of extensive outbreaks of acute infectious disease which may be regarded as truly epidemic, two points are outstanding. First, there is invariably evidence of direct spread from person to person; second, if the exciting cause is a readily demonstrable

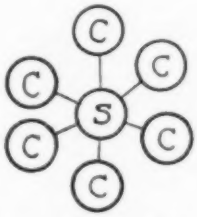


Fig. 2.—Mass infection.

one some alteration in the type of parasitism of the organism in the community as a whole can be determined. In a fulminating epidemic of meningitis, for example, there is clinical evidence of contact between patients and also a great increase in the general meningococcus carrier rate even among healthy noncontacts. The epidemic, in short, is associated with a fundamental upset in the "normal" type of parasitism of the causal organism. A similar state of affairs has been found in highly epidemic streptococcus infection in the military camps, in diphtheria and other infections.

In contrast to the foregoing, a widespread outbreak from a common source which is not an epidemic is shown in Figure 2.

The condition represented in Figure 2 might be illustrated by a water-borne outbreak of typhoid fever.

In sporadic disease, on the other hand, in its purest form conditions are quite different from those obtaining in a true epidemic. There is no spread from case to case, but each instance of the disease arises from a distinct source, such as a chronic carrier. Furthermore, there is no

evidence of any alteration in the general state of parasitism of the exciting organism in the community at large. Special susceptibility of the person is important rather than (possible) increased virulence of the bacteria. Figure 3 illustrates pure sporadic disease.

Obviously there are transition stages between pure sporadic and true epidemic disease in which a variety of sources may give rise to small groups of cases, no individual unit acquiring great potential.

In the present outbreak of tonsillitis these possibilities deserved consideration:

1. A true epidemic with spread from case to case. This possibility was ruled out by (*a*) absence of demonstrable clinical contact between successive or coincident cases, and (*b*) by the variety of strains of streptococcus concerned.

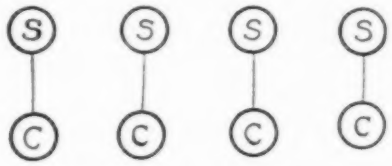


Fig. 3.—Pure sporadic disease.

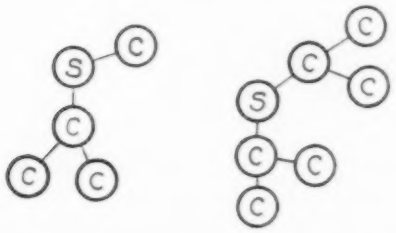


Fig. 4.—Transition stages between pure sporadic and true epidemic disease.

2. A common infection from a single source such as a carrier. This possibility was ruled out by the multiplicity of strains.

3. Infection of successive persons from a series of distinct sources, such as a group of carriers. This was undoubtedly the case in the present outbreak, as is shown by the following facts:

1. The known presence in the group of a large number of potential sources of infection in the form of chronic streptococcus carriers.

2. The absence of evidence of contact between cases.

3. The fact that a variety of strains (at least four) were concerned with the production of the disease.

4. The absence of any alteration in the general type of streptococcus parasitism in the group as a whole when streptococcus disease became prevalent as has been pointed out in a previous paper.[8]

In brief, then, despite the large number of cases, the outbreak consisted of multiple instances of sporadic infection, as illustrated in

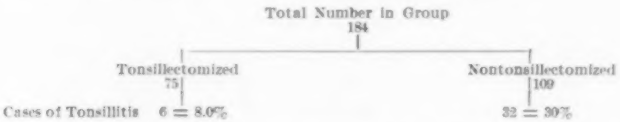
Figure 3. One might picture, on the one hand, a variety of possible sources of infection (carriers) in close contact with a group of susceptible people on the other. The exact nature of susceptibility cannot be defined completely as yet, but in the present instance it has been possible to determine at least three factors, which will be discussed in the following section.

FACTORS CONCERNED IN RESISTANCE TO ACUTE TONSILLITIS

An attempt was made to analyze further the factors which seemed to promote infection on the one hand or to decrease susceptibility on the other.

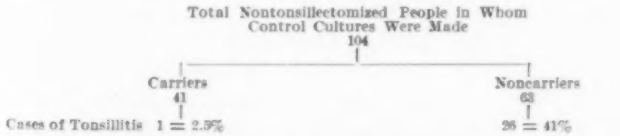
1. Relation of tonsillectomy to occurrence of acute streptococcic lymphadenoid infection of the throat. It soon became apparent that the incidence of infection was lower in those members of the group whose tonsils had been removed. Of the 184 subjects, 109 possessed their tonsils, whereas in seventy-five cases, they had been removed. Among the former there were thirty-two instances of tonsillitis, an incidence of 30 per cent.; among the latter, there were six cases, an incidence of 8 per cent.

The occurrence of "tonsillitis" in tonsillectomized and nontonsillectomized members of the group is represented below.



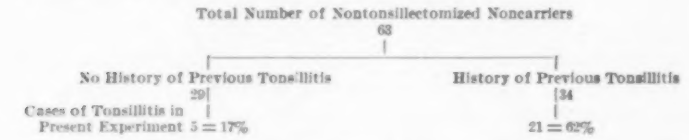
It appears, then, that tonsillectomy definitely renders a person less susceptible to acute streptococcic infection of the lymphadenoid tissue of the throat, and the explanation seems obviously an anatomic one.

2. The relation of the streptococcus carrier state to susceptibility to tonsillitis. As pointed out above, it was striking that those persons who already were tonsil carriers of the human type beta hemolytic streptococcus failed to develop tonsillitis during the course of the present experiment except in one instance. The incidence of tonsillitis in carriers and noncarriers is presented graphically in the diagram.



It appeared, therefore, that streptococcus carriage furnished a sound index of the likelihood of a person developing tonsillitis. The question remained open, however, whether the presence of the streptococcus in

itself conferred protection, or whether the streptococcus merely indicated some other or previous reaction, such as an attack of tonsillitis, which had led to the development of a certain degree of immunity. It was decided to test the latter hypothesis on the following supposition: If the presence of streptococcus in itself was not responsible for protection, and if lack of susceptibility were due to protection conferred by passing through an attack of tonsillitis of which the streptococcus was merely an indication, then the more recent the attack of tonsillitis the greater one would expect the protection to be. The group of sixty-three nontonsillectomized noncarriers was therefore analyzed in regard to the relation of history of previous tonsillitis to occurrence or nonoccurrence of tonsillitis during the course of the present experiment. The results are shown in the following diagram:



The results are the opposite of what would be expected if the previous attack of tonsillitis conferred protection apart from continued carriage of streptococcus. In other words, of those people who are not carriers at a given time, those who have never had tonsillitis and therefore have probably never been carriers are less susceptible; conversely, it must be concluded that in so far as insusceptibility runs parallel to streptococcus carriage such insusceptibility must depend directly on the presence of the streptococcus. One may think of the carried organisms as keeping up a sort of chronic vaccination, the protective effects of which wear off rapidly when the carriage ceases. This view is supported by the facts presented in Table 4, which shows the interval elapsing between the present attack and the preceding one. It is seen that in a good many cases the streptococci had disappeared and immunity had worn off within a few months to two years after the previous attack.

3. "Natural" resistance. A further examination of the diagram indicates that people with no history of tonsillitis in the past showed much less tendency to develop the disease in the present experiment than a similar group with positive past history. This would seem to mean that certain persons possess naturally a lower degree of susceptibility to this type of streptococcus infection than others. Whether this relative degree of immunity is inherent and natural, whether it is acquired in an unrecognizable way, or whether it depends on anatomic conditions, it does not seem profitable to discuss at the present time. At any rate, the fact is definite, and for clinical purposes may best be

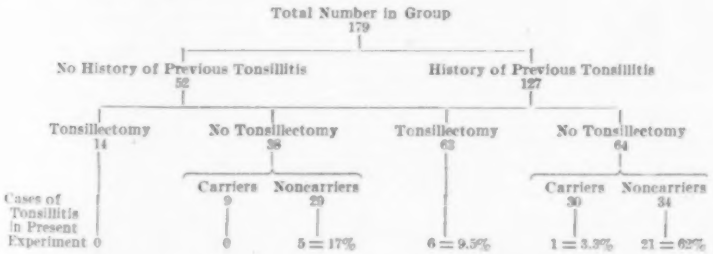
expressed by saying that if a person reaches the age of 20 years (approximately) without having had tonsillitis, the chances of acquiring the infection later are relatively slight.

The entire question of susceptibility, as brought out in the present study, may then be summarized as follows: In a group of young adults there are a certain number who seem to be "naturally" insusceptible or relatively insusceptible to acute streptococcic infection of the lymphoid

TABLE 4.—*Interval Between Present and Previous Attack of Tonsillitis*

Case	Previous Attack	Present Attack	Interval
19	August, 1922	December, 1922	4 months
13	February, 1922	November, 1922	9 months
10	November, 1921	October, 1922	11 months
24	1922	1923	12 months
32	February, 1922	February, 1923	12 months
20	November, 1921	March, 1923	16 months
37	October, 1921	February, 1923	17 months
34	October, 1921	February, 1923	17 months
22	March, 1921	January, 1923	22 months
31	February, 1921	February, 1923	2 years
14	1920	1922	2 years
15	1920	1922	2 years
28	1919	1923	4 years
1	1917	1922	5 years
27	1913	1923	10 years
29	1913	1923	10 years
11	1908	1922	14 years
26	Childhood	1922	15 plus years
16	"Years ago"	1922	? years
4	"None recently"	1922	? years

tissue in the throat. Such insusceptibility is enhanced by tonsillectomy, and in any case tonsillectomy confers a high degree of protection. Among people not naturally insusceptible, a temporary protection is conferred by the carriage of streptococcus following an acute infection. The subsidence of the carrier state in this group is, however, followed by a prompt increase in susceptibility. All the factors are assembled in the following diagram:



History	Tonsillectomy	Carriage	Number of People	Incidence of Tonsillitis
0	+	0	14	0
0	0	+	9	0
+	0	+	30	3.3%
+	+	0	63	9.5%
0	0	0	29	17.0%
+	0	0	24	62.0%

SUMMARY

1. In the present series of cases acute follicular tonsillitis was uniformly due to the beta hemolytic type of streptococci.

2. Following the acute disease, the organisms persist for an indefinite length of time in the tonsils.

3. Evidence is presented to show that a large outbreak of tonsillitis was not a real epidemic but a group of sporadic cases.

4. Tonsillectomy confers a high degree of protection against acute streptococcic infection of the lymphoid tissue of the throat.

5. A certain number of persons in a group seem "naturally" insusceptible or relatively insusceptible to tonsillitis.

6. Tonsillitis is not as a rule an autogenous infection but occurs in people not already carriers of hemolytic streptococci.

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING OCCLUSION OF THE LEFT CORONARY ARTERY *

FRED M. SMITH, M.D.

CHICAGO

In 1918, an investigation [1] was reported in which an electrocardiographic study was made on the dog following the ligation of the coronary arteries. The changes in the T-deflection subsequent to the closure of branches of the left coronary artery were the most constant findings. Immediately following the ligation, this deflection became more prominent, and the height that it assumed apparently depended on the degree to which the circulation to the left ventricle was disturbed. After the closure of the descending or circumflex branches the amplitude of the T-wave occasionally approached and in a few instances even exceeded that of the R-deflection. The increase in the amplitude of the T-wave has repeatedly been observed in later work in which it was necessary to ligate branches of the left coronary artery.

Within twenty-four hours the T-deflection became sharply negative. The extent to which this wave became a negative phase and the duration of this state likewise seemed to depend on the size of the vessel ligated. Following the closure of either of the main branches of the left coronary artery, the T-wave usually became negative in each of the three leads and remained in this condition for three or four days. The extent of the downward deflection gradually became less, and by the sixth or eighth day had changed to a positive phase in lead I, later in lead II and finally in lead III. The order of the derivations in which the T-wave changed to an upward deflection was occasionally reversed.

The negative feature of the T-deflection was checked up in a subsequent investigation.[2] In those instances in which the T-wave failed to become negative following the ligation of branches of the left coronary artery there was an extensive collateral circulation which had almost eliminated the formation of an area of infarction.

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* Read before the American Society for Clinical Investigation, Atlantic City, N. J., April 30, 1923.

* From the Department of Medicine of Rush Medical College and the Presbyterian Hospital.

1. Smith, Fred M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

2. Smith, Fred M.: Further Observations on the T-Wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, Arch. Int. Med. **25**:673 (June) 1920.

The decrease in the amplitude of the QRS group that followed the ligation of the branches of the left coronary artery was only casually mentioned in the first report. The curves taken during this investigation have since been reviewed. It was noted that ten animals recovered from the ligation of the descending branch, six the circumflex branch of the left coronary artery and thirteen the combined closure of one or more branches of these two vessels. The electrocardiograms of twelve showed a diminished amplitude of the QRS group. This change in the electrocardiogram followed the closure of the circumflex in six (100 per cent.), the descending branch of the left coronary in two (20 per cent.) and the branches of each of these arteries in four (30 per cent.).

The change in the amplitude of the initial ventricular deflections was observed as early as the second day after the operation. In some it persisted until necropsy. In others the height of the deflections gradually returned to normal after two or three weeks.

During the time of the initial investigation, a patient consulted Dr. Herrick,[3] in whom he made a diagnosis of coronary thrombosis which was later verified by necropsy. This patient was first seen fifteen days following the coronary accident. The electrocardiogram showed a sharp negative T-deflection in leads I and II. Ten days later the T-wave was less negative in leads I and II. In the curve taken after a period of five months the amplitude of the QRS group was very low. In the meantime, the patient had another attack of severe precordial pain which lasted for several hours. At necropsy the descending branch of the left coronary artery and one of the main descending branches of the circumflex were occluded. The thrombosis of the latter vessel was of recent origin. There was an extensive fibrosis of the endocardial and subendocardial layers which extended from the apex upward and involved the papillary muscles.

Since Dr. Herrick's report, Pardee,[4] Robinson and Herrmann[5] and Kahn[6] have observed changes in the T-deflection following coronary occlusion in man. The initial electrocardiogram was taken of the patient reported by Pardee about two hours after the onset of the cardiac pain. The T-wave was very prominent in leads II and III and arose from the descending limb of the R-peak. A few days later the T-deflection was a sharply negative phase in the corresponding

3. Herrick, J. B.: Thrombosis of the Coronary Arteries, J. A. M. A. **72**:387 (Feb. 8) 1919.

4. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**:224 (Aug.) 1920.

5. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, Heart **8**:59, 1921.

6. Kahn, M. H.: Aneurysm of the Left Ventricle, Am. J. M. Sc. **163**:839, 1922.

leads. Two of the patients studied by Robinson and Herrmann gave electrocardiograms in which the final ventricular deflection was negative after the coronary accident. In the one whom frequent curves were taken, the transition in the form of the T-wave was similar to that produced experimentally in the dog.

Wearn [7] has recently reported a study of nineteen cases of cardiac infarction which came to necropsy. In ten, electrocardiograms were taken. In eight, only one record was made. Wearn noted that the disturbance in the T-wave and a decrease in the amplitude of the QRS deflections were the most constant findings. In all ten patients there was an alteration of the T-wave in at least one lead. He particularly mentioned the frequency of the change in this deflection in leads I and II. In one, the T-wave in lead II arose from the descending limb of the R-deflection as in the patient reported by Pardee. This curve was taken on the first day after the onset of the cardiac accident.

The amplitude of the QRS waves was diminished in the curves of five of the ten patients. In some instances this feature was so marked that the deflections were almost iso-electric.

CORONARY OCCLUSION IN MAN

This report is based on the electrocardiographic findings of eleven patients. In one, the descending branch of the left coronary artery was ligated in the repair of a self-inflicted stab wound of the heart. The remaining ten had the typical clinical manifestations of coronary artery occlusion. In two the diagnosis was verified at necropsy. Eight recovered from the attack. In eight of these eleven patients, three or more electrocardiograms were taken.

Case 1.—H. S.,[8] aged 44, entered the Cook County Hospital on Aug. 3, 1920. Shortly after entering the hospital he attempted suicide by stabbing himself in the precordial region with a sixteen penny casing nail. He was found by the intern in a state of collapse and rushed to the operating room. Dr. George L. Davenport exposed the heart under local anesthesia and found blood spurting from a wound in the heart just to the left of the descending branch of the left coronary artery at the level of the middle third. In the repair of the wound Dr. Davenport found it necessary to ligate the artery. The patient made an uneventful recovery. On the nineteenth day following the operation the patient reported to the Presbyterian Hospital for an electrocardiogram. The T-wave (Fig. 1 *a*) was negative in each of the three leads. The second curve (Fig. 1 *b*) was taken seventeen days later. The final ventricular deflection was less negative. The third electrocardiogram (Fig. 1 *c*), which was taken fifty-nine days after the operation, was similar to the second. The fourth record was made nine months after the operation. At this time the T-wave was a positive phase in the leads I and II.

7. Wearn, J. T.: Thrombosis of the Coronary Arteries with Infarction of Heart, Am. J. M. Sc. **165**:25, 1923.

8. This patient is to be reported more in detail by Dr. Davenport.

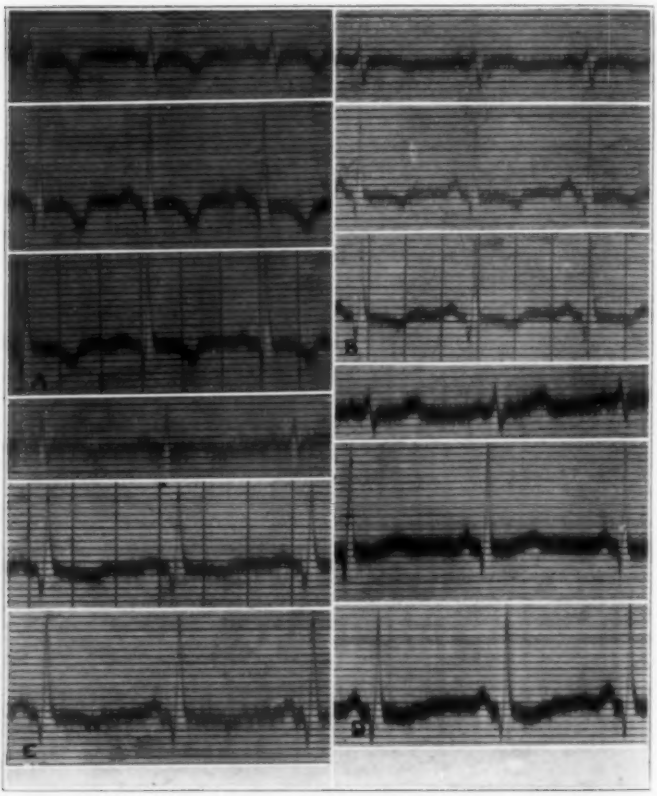

Fig. 1 (Case) 1.—*a*, electrocardiogram taken nineteen days after the ligation of the descending branch of the left coronary artery. The T-wave is a sharply negative deflection in the three leads; *b*, taken thirty-six days following the operation. The T-wave is less negative than in the previous curve; *c*, taken fifty-nine days after the ligation. The T-deflection is still slightly negative; *d*, curve taken eight and one-half months following the ligation. The final ventricular deflection has changed to a positive phase in leads I and II and to an iso-electric state in lead III.

CASE 2.—M. F., aged 51, entered the Presbyterian Hospital in the service of Dr. Irons on Jan. 25, 1923. He complained of severe precordial pain and shortness of breath. He stated that the pain first appeared while on the way to his business about 9:30 in the morning. It became so severe that he was compelled to stop in a drug store for relief. While here he collapsed and was taken to the hospital. When he reached the hospital the pain was very severe and radiated to both arms. There was in addition to the pain a sensation of great heaviness and constriction in the chest. He was compelled to sit up because of the shortness of breath. The patient was seen by Dr. Irons soon after he entered the hospital, about 11:30 a. m. He was given, hypodermatically, morphin sulphate, ¼ grain. The pain, however, continued through the afternoon and evening and morphin was repeated. Shortly following the second hypodermic administration of morphin the patient went to sleep and had a fairly good night. He, however, awakened in the morning with the same precordial distress. It gradually became less severe during the morning and had entirely disappeared by 10:30.

When the patient was first seen by Dr. Irons the pulse rate was about 90 per minute, and the quality was fair. The left cardiac dulness was slightly outside the midclavicular line. The heart tones were faint. There was no definite murmur, and the rhythm was regular. The following morning the patient had a short attack of rapid but regular action of the heart. Soon after the attack the heart was examined. A definite systolic apical murmur was noted. The left cardiac dulness was well outside the midclavicular line. The other physical findings were negative.

The first electrocardiogram (Fig. 2, *a*) was taken at 4:45 p. m. of the same day that the patient entered the hospital. The T-wave was slightly negative in the first lead. The following morning at 9:30 the T-deflection (Fig. 2, *b*) was markedly negative in lead I and iso-electric in lead II. A curve Fig. 2, *c*) taken at 2:30 p. m. on the second day showed sharply negative T-waves in the first and second leads. There was at this time a definite decrease in the amplitude of the QRS-deflections. The following day the T-wave (Fig. 2, *d*) was still negative in lead I but had changed to an iso-electric state in lead II. The amplitude of the QRS group had increased. The curves (Fig. 2, *e* and *f*) taken on the two succeeding days were similar to the latter. At this time the patient had begun to feel better, and left the hospital against the advice of the physician.

CASE 3.—A. D. L., aged 39, entered the Presbyterian Hospital on Feb. 15, 1922, in the service of Dr. Vernon David for hemorrhoidectomy. The following morning while in the operating room he experienced a severe pain in the substernal region, associated with a feeling of heaviness. The distress gradually increased in intensity and radiated to the arms. The pulse became rapid and irregular. The pain continued until the following morning. During this time the patient had received heroin hydrochlorid, 1/12 grain, morphin sulphate, 1/6 grain, and several doses of nitroglycerin, 1/100 grain, without complete relief from the distress. He was seen at this time by Dr. Dick. The left cardiac dulness was well outside the midclavicular line. A soft systolic apical murmur was heard, and there was a gallop rhythm. The cardiac rate was 130 a minute. A diagnosis of probable coronary occlusion was made. The cardiac findings remained about the same for the following ten days, except for periods of marked irregularity which were apparently due to the frequent appearance of premature contractions. During this time there was an occasional complaint of precordial distress. On March 4, the gallop rhythm had disappeared. There was still a short murmur over the apical area. The patient seemed to feel well and was permitted to sit up on a back rest. Four days later he died while asleep. At necropsy the descending branch of the left coronary artery and two of the smaller branches of the circumflex were found occluded. The pathologic findings in the layers of the myocardium were essentially the same as in the patient whose case was reported by Dr. Herrick.

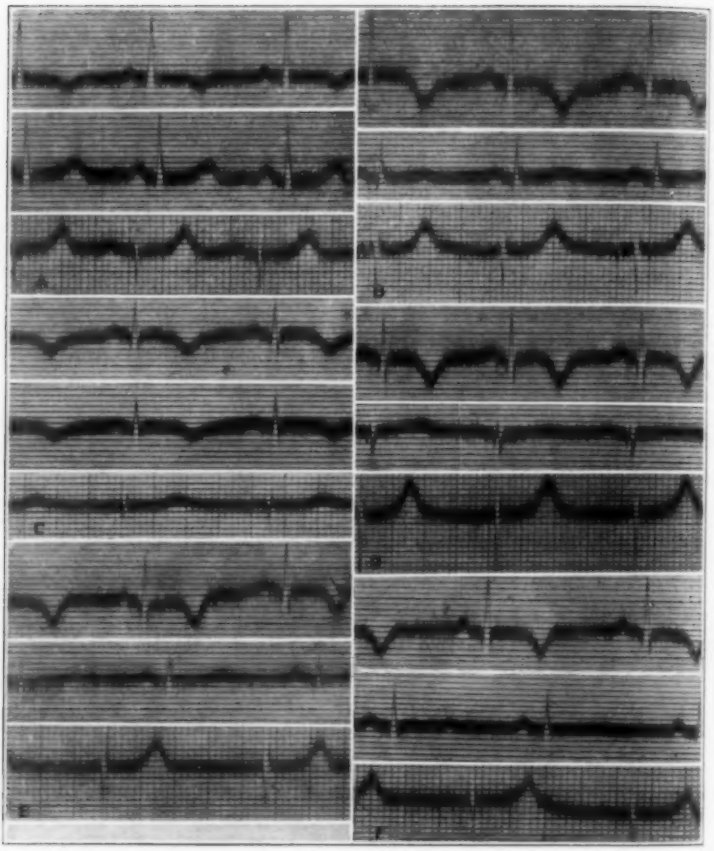

Fig. 2 (Case 2).—*a*, this curve was taken six hours after the onset of a severe attack of precordial distress. The pain lasted about twenty-four hours. The T-wave is slightly negative in lead I and positive in leads II and III; *b*, curve taken at 9:30 the following morning. There has been a definite change in the T-deflection in leads I and II. In the former it is more negative; in the latter it is almost iso-electric; *c*, taken at 2:30 p. m. of the same day. The T-wave has changed to a negative phase in lead II and is less positive in lead III. There is in addition a definite decrease in the amplitude of the QRS group; *d*, taken on the third day following the cardiac accident. The T-waves are similar to those shown in *b*. The S-wave in lead II has become more prominent than the R-peak. There has been marked increase in the amplitude of the S-deflection in the third lead; *e*, taken on the fourth day after onset of pain. The T-deflection is similar to that in *d*. The chief ventricular deflection in lead II has changed to a positive phase and the S-wave in lead III is less prominent; *f*, taken on the fifth day; similar to *e*.

The first electrocardiogram (Fig. 3, *a*) was taken on the morning following the onset of the pain. He still had distress. The curve showed what is ordinarily considered a right bundle branch conduction defect. The T-wave was diaphasic in lead I and moderately prominent in leads II and III. Three days later the T-deflections (Fig. 3, *b*) were iso-electric in the three leads. The T-wave in the curve taken eleven days after the second record (Fig. 3, *c*) was negative in the first and second leads and the amplitude of the QRS group markedly diminished.

Case 4.—G. B. M., aged 42, entered the Presbyterian Hospital on Nov. 8, 1921, in the service of Dr. Irons. A few days prior to entering the hospital the patient had had a series of attacks of severe precordial pain which radiated to the arms and neck. These attacks apparently came on without exertion or excitement. The last appeared shortly after eating lunch, and

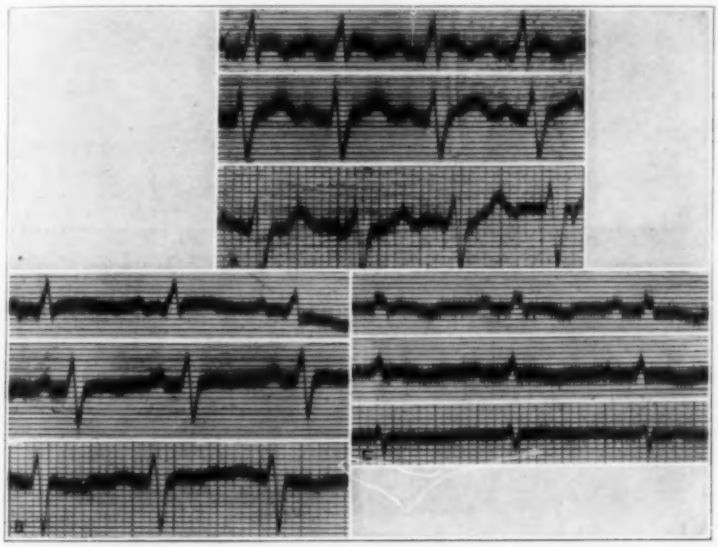

Fig. 3 (Case 3).—*a*, in this patient the diagnosis of coronary thrombosis was verified by necropsy. The curve was taken twenty-four hours after onset of cardiac pain. The patient still had pain at the time the record was made. The electrocardiogram resembles that of a right bundle branch block; *b*, taken four days following the cardiac accident. The T-wave is practically iso-electric in the three leads. There has been little change in the other ventricular deflection; *c*, taken eleven days later, fifteen days after onset of pain. The amplitude of the QRS group is markedly diminished. The T-deflection is negative in leads I and II.

the patient beecame nauseated. In one attack, the distress lasted for about sixteen hours. Following the last attack the patient felt weak and the heart became rapid. Two days later he came to the hospital. At this time he was short of breath on the slightest exertion. The left cardiac dulness was just inside the anterior axillary line. There was a systolic apical murmur, and the rhythm was frequently interrupted by premature beats. A friction rub was noted over the lower sternum. The systolic blood pressure was 102,

whereas it had previously varied from 140 to 160. The patient remained in the hospital for almost five months. During most of this time his heart was in a critical condition. He had a persistently rapid cardiac rate. There was a gallop rhythm. He had frequent periods of cardiac irregularity, and at one time had an attack of rapid regular heart action which lasted for several hours. The patient was finally discharged April 2, 1922. He was at this time able to be up and was permitted to take a little exercise.

The first electrocardiogram (Fig. 4, *a*) was taken two days after the patient entered the hospital. The ventricular deflections were very low in each lead. Five weeks later the amplitude of the QRS group (Fig. 4, *b*) had increased and the S-deflection in lead III was most prominent. The T-wave is iso-electric in the three leads. The curve (Fig. 4, *c*) taken in October, 1922, showed a left ventricular preponderance with a prominent R and S-deflection. The T-wave was iso-electric in lead I and positive in leads II and III.

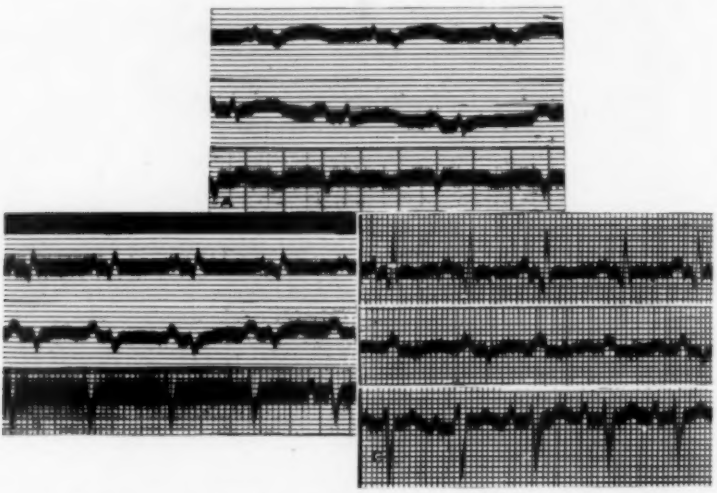

Fig. 4 (Case 4).—*a*, curve taken twelve days after a sudden and severe cardiac upset. The amplitude of the QRS group is low in the three leads. The T-wave is slightly positive in leads I and II; *b*, taken thirty-three days following the first curve. The S-deflection in lead III has become much more prominent. The chief ventricular wave has remained low in leads I and II. The T-wave is practically iso-electric in the three derivations; *c*, taken eleven and one-half months after cardiac accident. The curve is that of left side preponderance. The T-wave is positive in leads II and III and iso-electric in lead I.

Case 5.—R. S., aged 63, entered the Presbyterian Hospital on June 1, 1922, in the service of Drs. Irons and Greer. He gave a history of having had a high blood pressure for ten years. His general health, however, had been fairly good during this time, and a few days prior to the onset of the present illness he had been doing fairly heavy physical work without discomfort. During the two days before entering the hospital he had had several attacks of precordial distress which were associated with weakness and shortness of breath. One of these attacks lasted about nine hours, during which the patient was very dyspneic and exhausted. One was accompanied by nausea and

vomiting. At the time the patient entered the hospital he was very weak, short of breath on the slightest exertion and still complained of pain in the chest. The lips were slightly cyanotic. The left cardiac dulness was just inside the anterior axillary line. The heart rate was 130 a minute with a pulse deficit of 40. The rhythm was irregular. The cardiac tones were indistinct. No murmurs were detected. There was, however, a friction rub over the lower cardiac area. Moist râles were heard in the bases of the lungs. The liver was palpable and slightly tender. The systolic blood pressure was 110 and later 90, and the diastolic pressure was 55. The diagnosis of coronary

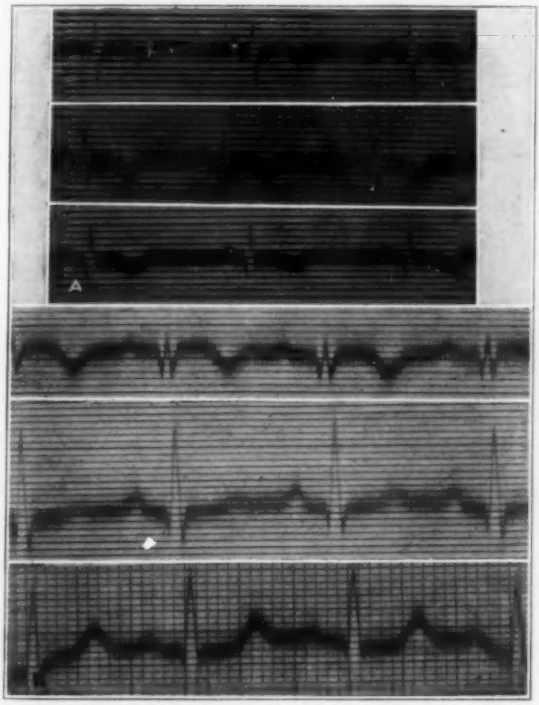

Fig. 5 (Case 5).—*a*, electrocardiogram taken three weeks after a severe attack of precordial pain which lasted for about twelve hours and was associated with great difficulty in breathing. The T-wave is sharply negative in lead I; *b*, taken six months later. The T-deflection now is practically isoelectric in lead I; *c*, curve taken four weeks after prolonged attack of severe cardiac distress. This patient died in a few weeks from cardiac failure. The T-wave is a sharp downward deflection in lead I. This feature is less marked in lead II, while in lead III the T-wave is positive.

thrombosis was made. The course was slowly progressively downward, and the patient died from cardiac failure on Aug. 15, 1922. At necropsy the descending branch of the left coronary was occluded. There was a large,

partially healed infarcted area in the apical region of the left ventricle with a parietal aneurysm. An electrocardiogram taken two weeks before death showed a decrease in the amplitude of the QRS group. The T-deflection was isoelectric in the three leads.

The important features of the histories of the remaining six patients were essentially the same. Each recovered from a severe attack of precordial pain which lasted from eight to twelve hours. The pain

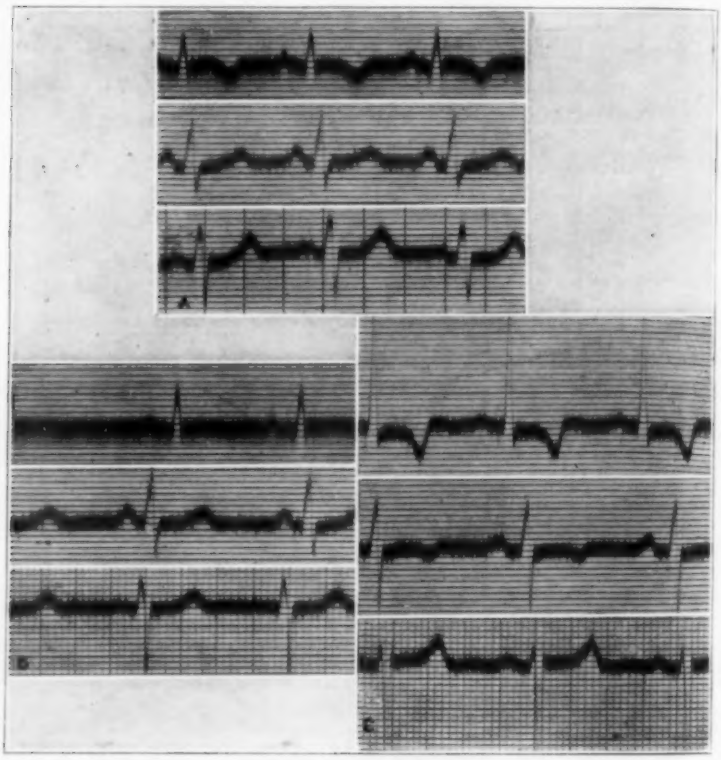

Fig. 6.—*a*, curve taken two weeks after an attack of precordial pain which lasted for about twelve hours and was not completely relieved by morphin. The T-wave is negative in each of the three leads and the amplitude of the chief ventricular deflection is moderately low; *b*, electrocardiogram taken one week following a severe attack of angina-like pain. The T-deflection in lead I is negative.

was referred to the arms and in some to the neck and was so severe that it was not entirely relieved by morphin. In all instances, the distress was associated with symptoms and signs of cardiac failure.

Three of these patients consulted Dr. Herrick one, two and five weeks, respectively, following the attack. In each a probable diagnosis of coronary occlusion was made. The electrocardiogram showed changes in the T-wave. In the one in which the curve (Fig. 5, *a*) was taken one week following the cardiac upset, the T-deflection was negative in the three leads. There was in addition a moderate decrease in the amplitude of the QRS group. The T-wave in the electrocardiogram (Fig. 5, *b*) of the patient seen two weeks after the attack was sharply negative in lead I. In the curve of the third patient the final ventricular deflection was slightly negative in leads I and II.

One of these patients made a satisfactory recovery and was not short of breath on moderate exertion when seen by Dr. Herrick. The other two had extensively damaged hearts. One was confined to bed for weeks because of cardiac failure. The other, at the time of the last report, had markedly impaired cardiac function.

The remaining three patients were followed in the outpatient department of Rush Medical College. They were first seen three, four and six weeks, respectively, following the cardiac accident. In two, the electrocardiogram showed changes in the T-deflection (Fig. 6, *a*, *b* and *c*). In the third, there was a moderate decrease in the amplitude of the chief ventricular deflection and an increase in the duration of the QRS group. Each had signs and symptoms of cardiac failure when first seen. Two died within a few weeks following their first visit to the clinic. The third is now 65 years old and is in a fair state of health. He has, however, carefully obeyed instructions and has never exerted himself beyond the point where he begins to feel winded.

COMMENT

The electrocardiographic findings of eleven patients are presented. In one, the descending branch of the left coronary artery was ligated in the repair of a stab wound of the heart. In two, the clinical diagnosis of coronary thrombosis was verified at necropsy. In the remaining eight patients, the character and duration of the cardiac pain and the subsequent clinical course was as characteristic of coronary closure as in those in whom the diagnosis was checked by necropsy. It would thus seem that we were reasonably justified in making the diagnosis of coronary occlusion.

In eight of the eleven patients, the electrocardiograms showed changes in the T-deflection. In two, the T-wave was sharply negative in lead I; in four, in leads I and II; and in two, in each of the three derivations. In four, the electrocardiograms showed progressive changes in the final ventricular deflections. In the patient in whom the descending branch of the left coronary artery was closed by operation, the T-wave of the first electrocardiogram (Fig. 1, *a*) was negative

in each of the three leads. In later curves (Fig. 1, *b* and *c*), this wave became less negative and finally changed to a positive deflection (Fig. 1, *d*). The most striking alteration in the T-wave (Fig. 2, *a* and *f*) was noted in the second patient in whom the first curve was taken on the same day as the cardiac accident and daily thereafter during the period of hospitalization. One of the patients studied by Robinson and Hermann showed similar progressive changes in the electrocardiogram. The variations in the T-wave of the electrocardiogram (Fig. 3, *a* and *c*) of the third patient was definite but less characteristic.

In six patients, there was a decrease in the amplitude of the QRS group. In two, the amplitude was low (Fig. 3, *c* and Fig. 4, *a*). In one of these, the low deflection was noted in the first curve taken thirteen days after the onset of the cardiac accident. Nine months later, the heights of the QRS deflection had returned to normal (Fig. 4, *c*). In the other, the reduction in amplitude occurred some time between the third and fourteenth day after the coronary closure. In another instance, the change in height of the deflection was transient and noted first on the second day (Fig. 2, *c*). One patient had moderate reduction in amplitude of the initial ventricular waves in the record taken one week after the attack of cardiac pain (Fig. 5, *a*).

The foregoing changes in the T-wave and the amplitude of the QRS group resemble closely those in the dog following the ligation of the branches of the left coronary artery. These changes were most striking, and the resemblance to those of the dog were greatest in those patients in whom curves were taken early and at frequent intervals subsequent to the coronary accident. This is to be expected since the greatest changes occur in the heart during the first few days after the coronary closure. Curves taken at a later date may thus fail to show characteristic changes. This perhaps accounts for the negative findings in some of the cases which have been reported.

The negative T-deflection is the most constant and characteristic electrocardiographic findings following coronary closure. It is to be noted that the peak of this deflection is sharp. This feature persists throughout the change from negative to iso-electric phase and resembles closely the alteration in the T-wave produced experimentally by Wilson and Herrmann [9] by varying the degree of block of the right branch of the auriculoventricular bundle. The same type of T-wave may also be produced by changing the refractory period of the apical region of the left ventricle by cooling. It is not improbable that the alteration in

9. Wilson and Hermann: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of Dog, Heart **8**:229, 1921.

the final ventricular deflection following coronary occlusion is due to a change in the refractory period of a localized area of the left ventricle.

In the experimental animal, the extent to which the T-wave became a negative phase seemed to depend on the size of the area of infarction. The latter in turn is dependent on the size of the vessel occluded and the degree of collateral circulation established. The collateral circulation between the various branches of the left coronary arteries varies markedly in the dog. A corresponding variation in this respect may be expected in man. The changes in the T-deflection following coronary closure may also be influenced further by the development of interventricular conduction defect. This was noted in the dog and has been observed further in man.

A marked decrease in the amplitude of the QRS group following a prolonged period of precordial pain fully justifies the diagnosis of a serious cardiac accident. This type of electrocardiogram was associated with extensive myocardial change in the dog and followed the closure of the circumflex branch of the left coronary artery in all instances in which the animal survived the operation. The patient reported by Dr. Herrick and one in our series who showed the foregoing electrocardiographic findings, came to necropsy. In each instance branches of the circumflex were occluded along with that of the descending branch of the left coronary artery. The other patient in our series had a severe and damaged heart. He was in the hospital for more than five months, and is again in a serious condition.

CONCLUSIONS

Experimental and clinical observations justify the belief that the electrocardiograph may be employed to advantage in the diagnosis of coronary thrombosis in man. It is predicted that a large percentage of those who have an occlusion of the left coronary artery will show significant changes in the electrocardiogram within the first few days following the cardiac accident. In some instances, the alteration in the electrocardiogram may persist for weeks. Changes in the T-deflection and a decrease in the amplitude of the QRS group are the most constant findings. The former is apparently dependent on the formation of an area of infarction in the apical region of the left ventricle. The latter has been associated with more extensive and disseminated changes in the myocardium.

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STUDIES ON THE RABBIT'S HEART*

I EFFECT OF STROPHANTHIN ON THE SIZE OF THE NORMAL AND OF THE ABNORMAL HEART

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Clinical studies on the changes in the size of the heart are frequently difficult to control. A patient with cardiac decompensation lends himself poorly to the manipulation necessary for roentgen-ray studies, and furthermore, fluid in the chest frequently renders accurate measurements of the heart difficult. There are, therefore, few exact studies on the changes in the size of the decompensated heart that may occur in response to treatment; neither has the experimental study of this problem been sufficiently investigated. It is generally recognized, following the work of Fleischer and Loeb [1] and Walker,[2] that a chronic myocarditis can be produced in rabbits by the repeated injection of spartein sulphate and epinephrin chlorid. Fraser [3] further showed that a permanent enlargement followed repeated injections of these drugs. It occurred to us that this offered a means of studying the effect of various measures on the damaged heart, and the study of the effect of strophanthin was therefore undertaken. Vaquez and Dimitrakoff [4] are of the opinion that strophanthin (ouabain) intravenously caused a definite decrease in the size of the decompensated heart. Their work has been entirely clinical and as such is somewhat difficult to control. We hoped to investigate the problem experimentally.

We have attempted to produce a chronic myocarditis in rabbits by means of repeated injections of spartein sulphate and epinephrin chlorid,[5] and have followed the changes in size by roentgen-ray studies. Sixteen rabbits were injected, seven of which died before any marked change had occurred; of the remaining nine rabbits, six have shown

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1. Fleisher, M. S., and Loeb, L.: Experimental Myocarditis, Arch. Int. Med. **3**:78 (Feb.) 1909.
2. Christian, H. A.; Smith, R. M., and Walker, I. C.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**:469 (Oct.) 1911.
3. Fraser, F. R.: J. Exper. M. **22**:292, 1915.
4. Dimitrakoff: Thèse, Paris, 1922.
5. Footnote 1, 2 and 3.

definite increase of their heart shadow on the roentgenograms. The method we employed was as follows; for the first eleven rabbits we injected 25 mg. of spartein sulphate dissolved in 0.4 to 0.5 c.c. of distilled water, followed in from seven to ten minutes by 0.1 c.c. of epinephrin chlorid; for the remaining five rabbits we used an amount of spartein sulphate equivalent to 12 mg. per kilogram of body weight, followed by 0.1 to 0.15 c.c. of epinephrin chlorid. All injections were made intravenously into an ear vein. The spartein sulphate employed was put up by Merck & Co., and the epinephrin chlorid was the 1 : 1000 solution prepared by Parke, Davis & Co. Care was used to have the epinephrin chlorid always in a freshly prepared solution. The injections were repeated weekly until a definite and permanent increase in the size of the heart had occurred, at which time the effect of intravenous injection of crystalline strophanthin was studied. The strophanthin used was a 1 : 1,000 solution prepared in ampules by Merck & Co. It was tested by us by the Hatcher method and found to have a rabbit unit (minimum lethal dose per kilogram) of 0.6 mg. (0.6 c.c.). The amount of strophanthin given in this study was 30 per cent. of this rabbit unit. This should approximate the therapeutic dose, as Levine [6] has shown that the toxic effect occurs when about 50 per cent. of the minimum lethal dose has been given, and the therapeutic dose should be somewhat less. This amount (30 per cent.) is about the equivalent of the dose used clinically. After the strophanthin, roentgenograms were taken at five, ten and fifteen minute intervals, the heart shadow showing the greatest change when compared with the roentgenogram taken just before the injection was chosen. Roentgen-ray films were obtained with the tube at a distance of 5 feet (152 cm.), using a current of 30 milliamperes backed up by a 4½ inch (11.4 cm.) spark gap with an exposure of seven seconds. This greatest change usually occurred after ten minutes, although in a few instances it was seen on the five or on the fifteen minute plate. To determine changes in size, the heart was outlined in pencil on the film, and this outline was traced on smooth white paper of uniform texture. The silhouettes were cut out and weighed, the weights being accurate to 0.1 milligram. We believe this to be more exact than other methods for comparing the size of heart shadows. This method was formerly used by Dr. A. E. Cohn. No changes were considered significant unless they were greater than 10 per cent.

EXPERIMENTAL WORK

As all of these experiments were conducted on the same plan, a summary of but one case will be included as an example.

6. Levine, S. A.: J. Exper. M. **29**:485, 1919.

Rabbit 14, weighing 2.7 kg., whose heart silhouette weighed 60.9 mg. (Fig. 1), was given weekly intravenous injections of spartein sulphate, 32 mg. (dissolved in 0.4 to 0.5 c.c. distilled water), followed in seven to ten minutes by 0.1 c.c. of epinephrin chlorid solution intravenously. From a roentgenogram taken on February 20, after five such injections, we obtained a silhouette weighing 85 mg., an increase of 39 per cent. over the original weight. On this day an intravenous injection of strophanthin (25 per cent. of the rabbit unit in this instance) caused a decrease in the size of the heart of 13 per cent. On March 2, after six injections of spartein sulphate and epinephrin, a roentgenogram (Fig. 2) showed a heart of such size that the silhouette weighed 105.8 mg., an increase of 75 per cent. over the original weight. Strophanthin

TABLE 1.—*Sparteinized Hearts with Definite Dilatation*

Experiment Number	Rabbit Number	Weight of Heart Silhouette in Milligrams at Beginning of Experiment	Number of Injections of Spartein and Epinephrin*	Percentage of Increase in Weight of Heart Silhouette Following Spartein and Epinephrin	Amount of Strophanthin in C.c.†	Weight of Heart Silhouette Immediately Before Strophanthin	Weight of Heart Silhouette Immediately After Strophanthin	Percentage of Decrease Due to Strophanthin
1	14	60.9	5	39	0.36	85.0	74.0	13
2	15	75.6	5	10	0.43	81.8	75.4	8
3	3	57.6	4	23	0.22‡	70.8	62.4	12
4	2	80.2	9	13	0.45	90.8	85.4	6
5	3	57.6	9	17	0.48	67.2	59.8	11
6	14	60.9	6	75	0.43	105.8	91.4	14
7	15	73.6	6	23	0.52	90.5	74.8	17
8	2	80.2	9	18	0.45	94.6	84.4	11
9	3	57.6	9	20	0.48	69.0	57.0	17
10	17	87.4	5	19	0.68	94.0‖	106.9	14§
11	16	67.2	6	14	0.43	76.6	68.8	10
12	14	60.9	6	83	0.43	111.6	97.2	13
13	17	87.4	6	27	0.68	111.2	106.4	4
14	16	67.2	6	18	0.43	78.2	70.4	10

In these tables the following symbols are used with the meaning indicated:
* Given at approximately weekly intervals.
† The amount of strophanthin used was 0.18 c.c. per kilogram. This equals 30 per cent. of the rabbit unit.
‡ Arnaud's ouabaine.
‖ After exercise to exhaustion. Heart possibly contracted.
¶ Twenty per cent. of rabbit unit.
§ Increase.

given intravenously on March 2 caused a decrease in size of 13 per cent. (Fig. 3). On March 6, the silhouette weighed 111.6 mg., an increase of 83 per cent. Strophanthin again caused a decrease of 13 per cent. It is remarkable, but probably not significant, that in this rabbit the strophanthin in each instance caused a decrease of 13 per cent. in the size of the heart. Electrocardiograms on March 7 showed the same form of curve as that obtained on January 8.

The accompanying tables give in detail the results obtained on intravenous injection of crystalline strophanthin.

The first table shows those cases in which a definite myocarditis had been produced, as evidenced by cardiac enlargement. In these cases there was a uniform response to the injection of strophanthin. The decrease

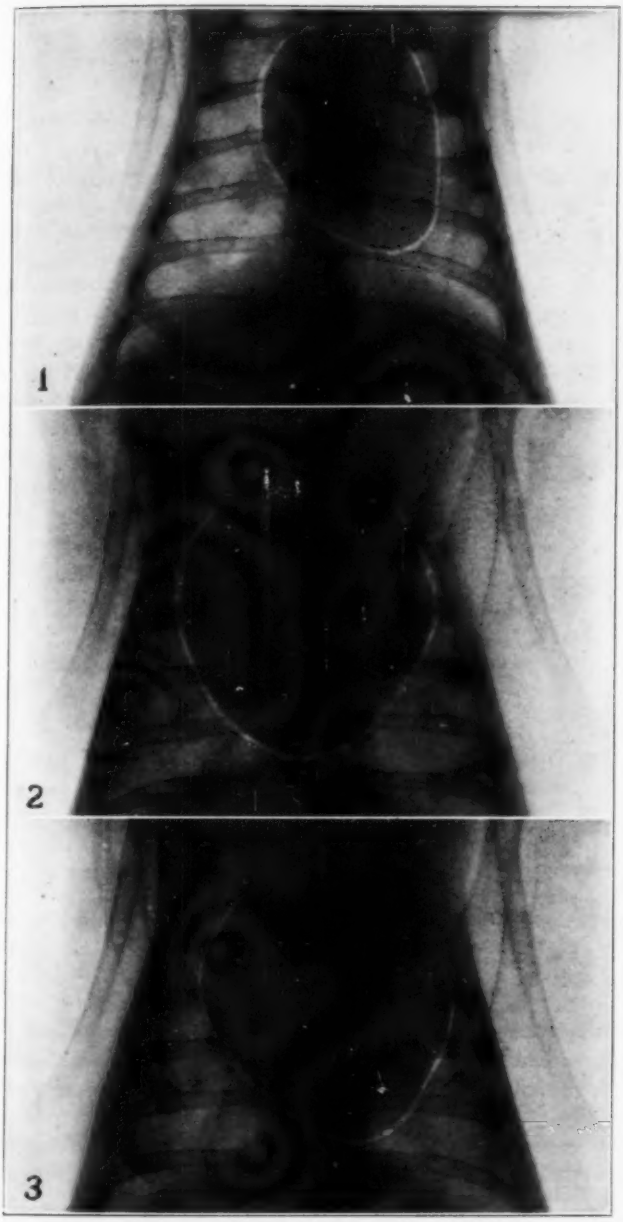

Fig. 1 (Rabbit 14).—Roentgenogram taken Jan. 9, 1923. The weight of heart silhouette was 60.9 mg.

Fig. 2 (Rabbit 14).—Roentgenogram taken March 2, 1923. The weight of the heart silhouette 105.8, a 75 per cent. increase over Fig. 1.

Fig. 3 (Rabbit 14).—Roentgenogram taken March 2, 1923, ten minutes after a 0.43 c.c. 1:1,000 strophanthin solution given intravenously. There was a decrease of 13 per cent. in size.

ranged from 4 to 17 per cent., with an average of 10 per cent. In one case (Experiment 10) there was an increase after injection of strophanthin. This rabbit had been exercised to exhaustion six hours previous to this experiment, and its heart may still have been somewhat contracted. Acute overexertion does cause definite decrease in the heart, as will be reported by us in another article.[7] This usually disappears in two hours. It may have persisted longer in this case. Subsequent injection of strophanthin caused a slight decrease in size in this case (Experiment 13). In these experiments we waited at least four full days after giving an injection of strophanthin before repeating it, so that no part of the first dose remained at the time the second dose was given.

TABLE 2.—*A, Normal Hearts*

Experiment Number	Rabbit Number	Weight of Heart Silhouette in Milligrams at Beginning of Experiment	Number of Injections of Spartein and Epinephrin*	Percentage of Increase in Weight of Heart Silhouette Following Spartein and Epinephrin	Amount of Strophanthin in C.c.†	Weight of Heart Silhouette Immediately Before Strophanthin	Weight of Heart Silhouette Immediately After Strophanthin	Percentage of Decrease Due to Strophanthin
15	19	61.6	0	0	0.21‡	61.6	62.4	1‡
16	20	61.1	0	0	0.48	61.1	66.0	8‡
17	21	81.0	0	0	0.52	81.0	77.2	5
18	22	70.0	0	0	0.43	70.0	76.0	8‡
19	19	61.6	0	0	0.48	58.4	50.8	13
20	7	68.2	0	0	0.43	71.2	53.6	25
21	8	61.6	0	0	0.36	48.6	67.0	38‡
				B, Sparteinized Hearts with No Dilatation				
22	9	71.0	4	0	0.22‡	72.4	70.4	2
23	9	71.0	9	0	0.50	70.4	64.8	8
24	10	70.3	9	0	0.45	66.2	73.0	10‡
25	11	65.4	8	0	0.25‡	61.0	51.0	18
26	18	76.0	5	0	0.50	60.4‡	64.0	6‡
27	9	71.0	9	0	0.50	72.2	63.0	13
28	10	70.3	9	0	0.45	66.2	58.8	11

In the second table are shown the results of strophanthin on normal hearts. Of these fourteen experiments, seven were performed on normal rabbits and the other seven on rabbits that had received injections of spartein and epinephrin but had shown no cardiac enlargement. These experiments show less constant results than in the case of the animals with dilated hearts. The average decrease in size was only 2 per cent. as compared with 10 per cent. for rabbits with chronic myocarditis.

The question is immediately raised, Is the decrease in size due to the strophanthin or to other factors? We know that physical exertion does decrease the size of the rabbit's heart. Care was used in putting the rabbit on the animal board so that it exerted itself as little as possible, and it was left absolutely quiet for two or three minutes before

7. Reported in Studies of Rabbit Heart II: "Effect of Vigorous Exercise on Size of Normal and Abnormal Rabbit Heart."

the first roentgenogram was taken. Then the strophanthin was injected and the five, ten, and fifteen minute plates were obtained. At no time after the strophanthin had been injected was the rabbit disturbed, except to insert new films under the back and to correct any faulty position. We feel that physical exertion has been effectively ruled out as the cause for decrease in the size of the heart. The possibility that an emotional influence might be responsible occurred to us. We therefore injected normal saline intravenously into two rabbits, using the same amount of fluid as was given in the strophanthin injections, and making all other details in the experiments identical. The hearts did not change appreciably in size; there was only a slight increase in one case and a slight decrease in the other case in the weight of the heart silhouettes after the saline. The changes were so small, 3.8 and 3.0 mg., respectively, that they are quite within the limit of error. It occurred to us to study the effect of spartein sulphate and epinephrin

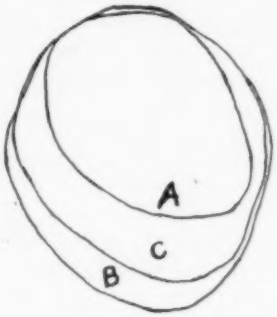

Fig. 4 (Rabbit 14).—Heart outlines superimposed for comparison. *A* is the outline of the heart in Fig. 1, showing the size at the beginning of the experiment. *B* is the outline of the heart in Fig. 2, showing the increase due to six injections of spartein and epinephrin. *C* is the outline of the heart after one injection of strophanthin.

chlorid when given during the routine treatments. The spartein sulphate had no effect on the size of the heart in three cases in which it was studied. This may be taken as added evidence that an emotional influence is not the cause of the decrease after the strophanthin. In five cases, the effect of epinephrin chlorid when injected in 0.1 c.c. amounts intravenously was observed. In each case there was an increase in the size of the heart; in three of the cases this increase was over 20 per cent. This increase following epinephrin came on earlier than the strophanthin effect and did not last so long. We feel that with these methods of controlling our results there can be little doubt that the decrease in size of the heart recorded in our tables is due to the effect of strophanthin on the heart muscle.

The postmortem examination of the rabbits studied revealed changes similar to those described by Walker.[2] The histologic changes were the production of cellular foci made up of lymphoid, plasma and young connective tissue cells, around necrosed or severely damaged muscle fibers, and the proliferation of connective tissue, sometimes quite extensive, replacing muscle fibers and extending into and separating the damaged muscle cells. The exact histologic picture varied with the age of the lesion; in the long standing cases a more extensive scar formation occurred.

This method of investigation, studying the responses of definitely damaged heart muscle to various procedures, offers, we believe, further possibilities. We hope to follow some rabbits with an experimentally produced myocarditis for a long period of time and to report subsequently on our findings.

CONCLUSIONS

1. Strophanthin given intravenously in doses comparable to those used clinically causes a definite decrease in size of the rabbit's heart.

2. This decrease is most marked in cases of experimentally produced myocarditis, as evidenced by cardiac dilatation. It also occurs to a certain extent in normal rabbits.

3. The heart usually begins to return to normal size at the end of fifteen minutes and always recovers completely after two hours.

STUDIES ON THE RABBIT'S HEART *

II. EFFECT OF VIGOROUS EXERCISE ON THE SIZE OF THE NORMAL AND THE ABNORMAL HEART

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AND
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By means of roentgen-ray studies and physical examination, certain observations have been reported on the effect of exertion on the size of the heart. We have been unable, however, to discover any reference to roentgen-ray studies on the hearts of animals subjected to vigorous exercise. Secher,[1] in 1921, reported some investigations on wild rats in which a group of eleven had been run until they died from the effects of exercise. From his observations, which consisted in measuring the hearts after death, he concluded that acute overexertion produced dilatation of the heart. Boigey [2] reported orthodiagraphic studies on competitors before and after a 42 kilometer Marathon race in which there was dilatation of the heart. In the same paper, he observed that contraction of the heart followed a 100 meter foot race. Dedichem [3] examined 226 participants before and after a 50 kilometer Marathon by means of palpation and percussion, but was unable to demonstrate any cardiac enlargement. The impression has been general that the first response to exercise was a decrease in size, followed after further exertion by a moderate dilatation.

In our studies, we selected a group of healthy rabbits which had been confined for some time in small animal cages. A group of "sparteinized" rabbits, reared under similar conditions, was also studied. These animals had received weekly intravenous injections of 25 mg. of spartein sulphate dissolved in distilled water, followed in from seven to ten minutes by 0.1 c.c. of a 1:1,000 solution of epinephrin chlorid. This technic was a modification of the procedures recommended by Walker [4] for producing a chronic myocarditis. These will be referred to as "sparteinized" rabbits. When there was definite enlargement of the heart, as evidenced by roentgen-ray films, the rabbits were considered to have a chronic myocarditis, the histologic findings of which

1. Secher, K.: Hospitalstidende **64**:49, 1921; No. 5, p. 65.
2. Boigey: Presse méd. **26**:657, 1921.
3. Dedichen: Acta Med. Scand. **53**:738, 1921.
4. Christian, H. A.; Smith, R. M., and Walker, I. C.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**: (Oct.) 1911.

Fig. 1 (Rabbit 16).—March 3, 1923; before exercise. The silhouette in this case showed an increase in weight of 20 per cent. over the weight of the silhouette made from the first roentgenogram of this animal on Jan. 11, 1923.

Fig. 2 (Rabbit 16).—March 3, 1923; showing a decrease in heart size of 28 per cent. after exercise.

have been seen in animals that have died or were killed during the course of the injections. The changes are those described by Walker.[4] Sixteen rabbits received such injections, nine of which were living when this study was undertaken. In three of the latter animals there was no evidence of cardiac enlargement.

The method we employed to exercise the rabbits to exhaustion was as follows: A squirrel-cage, treadmill type, a cylinder 4 feet (121.5 cm.) in diameter and 16 inches (40.64 cm.) in width, was constructed with smooth wooden sides and heavy wire-screen runway. This cage was operated by means of a simple crank. The outline plan consisted, first, in taking a roentgen-ray film [5] of the thorax while the rabbit was fastened on its back to the animal board. The rabbit was then placed in the treadmill which was revolved at a speed corresponding to the progress of the animal. The revolutions necessary to produce exhaustion averaged about twenty-two in number, and the procedure occupied

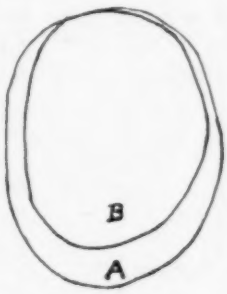

Fig. 3 (Rabbit 16).—Heart outlines superimposed for comparison. *A* is the outline of the heart in Figure 1. *B* is the outline of the heart in Figure 2, and shows the decrease due to exercise.

approximately three minutes. The animal was not removed until it showed evidence of marked exhaustion. It not only became limp, cyanotic (shown in the ears), markedly dyspneic, and unable to support itself, but it failed to react to ordinary stimuli, although, as pointed out later, the rabbits recuperated promptly and completely. Another roentgen-ray film was obtained as soon as the animal could be returned to the board. In a few cases we followed the recovery of the heart by frequent roentgen-ray plates. The heart shadow was outlined on the film with pencil, and a silhouette was traced from this on smooth white paper. This silhouette was carefully cut and weighed, the weight being accurate to 0.1 mg.

5. The film was taken with the tube at a distance of 5 feet (152 cm.), using a current of 30 millimeters backed up by a 4½ inch (11.4 cm.) spark gap with an exposure of seven seconds.

By reference to the table, it will be observed that all rabbits, both in the normal and in the two "sparteinized" groups, showed definite contraction of the heart. Two apparent exceptions (Experiments 2 and 3) occurred in which the animals failed to exercise properly. These animals subsequently showed definite contraction (Experiments 8 and 18). The average decrease of all cases was about 19 per cent., which is too large to be due to any possible error in our method of estimating changes in the size of the heart. From the table, it is apparent that there is no difference in the response to overexertion between the sparteinized animals showing increased heart size and those without

*Effect of Exercise to Exhaustion on the Size of the Heart**

Experiment Number	Rabbit Number	Date	Percentage Increase in Weight of Heart Silhouette After Spartein and Epinephrin	Weight of Silhouette Before	Weight of Silhouette After	Per Cent. Decrease in Size
A. Normal Hearts:						
1	7	1/13	..	58.0	49.6	14
2	8	1/13	..	52.2	55.4	6*Incr.
3	17	1/13	..	87.4	87.4	0*
4	18	1/13	..	76.0	60.0	21
5	19	3/ 3	..	56.2	48.7	13
6	20	3/ 3	..	62.6	52.6	15
7	21	3/ 3	..	81.4	67.0	17
8	7	3/ 3	..	64.8	54.0	16
9	8	3/ 3	..	53.0	37.2	29
B. Sparteinized Hearts Showing No Dilatation:						
10	2	1/13	..	77.2	56.6	26
11	3	1/13	..	60.3	48.4	20
12	9	1/13	..	72.0	60.0	16
13	10	1/13	..	69.2	56.4	18
14	18	3/ 3	..	77.6	60.6	22
15	9	3/ 3	..	67.2	57.2	15
16	10	3/ 3	..	64.0	51.8	19
C. Sparteinized Hearts Showing Dilatation:						
17	16	3/3	20	80.8	58.0	28
18	17	3/3	19	104.0	75.2	27
19	2	3/7	15	92.2	74.2	19
20	3	5/7	13	65.0	54.4	16
21	15	3/7	7	78.0	60.0	23
22	14	3/7	44	88.2	78.8	10
23	2	3/7	17	93.8	74.8	20
24	3	3/7	11	64.2	56.2	12

* These animals failed to exercise properly. In subsequent experiments the results were better.

enlargement. In part C. of the table, the fourth column from the left shows the amount of cardiac enlargement present when these experiments were performed, as judged by the percentage increase in weight of the heart silhouette. In those instances in which roentgenograms were repeated at intervals after exercise, there was observed a gradual return of the heart to normal size. Within two hours, this return was complete.

Following the exercise, the rabbit itself made a surprisingly quick recovery, and although it took two hours for the heart to return to normal size, the rabbit was apparently quite recovered in fifteen minutes. It was surprising that these animals suffered no obvious ill

effects from this overexertion (some of these rabbits have been under observation for two months following our first experiments). This was unexpected in the case of those rabbits with marked cardiac enlargement, due to a definitely damaged myocardium. We rather expected dilatation or at least no contraction in these animals after exercise. It would seem that these results emphasize the relative unimportance of merely objective findings in heart disease. Although these rabbits had one objective sign of an impaired heart, i. e., an enlargement, they apparently had sufficient cardiac reserve to enable them to respond to this acute overexertion in a normal way. Two of the animals with a definite myocarditis were exercised to exhaustion on March 7. Three hours later, when the hearts had returned to their normal size, the experiment was repeated and the response was the same.

CONCLUSIONS

1. Normal rabbits were exercised to complete physical exhaustion.
2. The result in every instance was a definite decrease in the size of the heart.
3. Six animals in which experimental myocarditis had been produced responded to overexertion in a similar manner.
4. Although the rabbits had been observed for only a comparatively short time, there was no evidence that acute overexertion influenced the general condition of the animals.

GIARDIA INTESTINALIS INFECTION *

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Giardia (Lamblia) intestinalis, discovered by Lambl in 1859, for a long time was considered a nonpathogenic parasite. It was believed to be rare in temperate climates and was regarded as an organism of negligible importance. Increased interest in this flagellate was awakened during the Great War, as numerous cases of intractable diarrhea were reported which were believed to be caused by this parasite. The English and the French, especially, believed it to be the etiologic agent in many cases of "trench diarrhea." Since the parasite had received but scant attention in the past, many interesting problems regarding its geographic distribution, pathogenicity and treatment presented themselves.

Giardia intestinalis differs from the other protozoa that inhabit the human intestinal tract in that its habitat is the duodenum and jejunum. The vegetative forms are readily detected in the duodenal contents in many cases in which the stools contain few or none of the cysts. Within the past few years, since the introduction of the Meltzer-Lyon method of duodenobiliary drainage, which includes the microscopic examination of the duodenal contents, many human carriers of this infection are being brought to light in temperate zones. Previously, when the diagnosis was made by the stool examination alone, many of these cases would have passed unobserved.

During the past two and one-half years, in performing duodenobiliary drainage on 170 patients, nine cases of infection by *Giardia intestinalis* were found. Eight of these patients were natives of Russia and Austria, but they were residents of New York City for many years. The ninth patient was a native and resident of New York City. It was not possible in any of the cases to discover when or where the infection originated. None of the patients had ever been in tropical countries.

Previous to these cases there are only two reports of this parasite on record in New York state. The first report is by DuBois and Toro,[1] in 1912, who reported four cases in children; the other is by Chace and Tasker,[2] in 1917, who reported three cases in adults. These

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1. DuBois, E. F., and Toro, W. C.: Two Cases of Infection with Lamblia-Intestinalis, Proc. N. Y. Path. Soc. **12**:32, 1912.

2. Chace, A. F., and Tasker, A. N.: The Diagnosis and Treatment of the Flagellate Diarrhoeas, J. A. M. A. **68**:1528 (May 26) 1917.

authors considered the infection rare. Stiles [3] reported the first American case in 1902. Following this, Allen [4] and Emerson [5] each reported one case. From various sections of the United States reports of cases have been made by Logan and Sanford,[6] McNeil,[7] Smithies,[8] Hemmeter,[9] Lyon,[10] Simon [11] and McGill.[12] Most of the cases were detected by stool examinations and many of them were associated with a diarrheal condition. Kofoid [13] found this flagellate in about 6 per cent. of 1,500 apparently healthy recruits coming from all sections of the United States. Maxcy [14] reports that *Giardia* infection is much more common in children than in adults. The infection has also been reported from most of the continental countries.

THE ORGANISM

An excellent and detailed description of this flagellate has recently been given by Simon.[15] Its appearance is quite characteristic. In brief, it may be described as a silvery colored body, from 10 to 20 microns in length and from 5 to 12 microns in width. In shape it resembles a pear split into two parts along the long axis. On the anterior half of the flat surface there is a cuplike depression, the sucking disk, or peristoma which is best seen in a lateral view. There are two nuclei anteriorly, which give the organism, when viewed on the flat surface, a comical, facelike appearance similar to that of a skate fish. There are eight flagella arranged in pairs. By means of the peristoma they attach themselves by suction to the epithelial cells

3. Stiles, C. W.: First American Case of Infection with Lamblia Duodenalis, Washington M. Ann. **1**:64 (March) 1902.
4. Allen, W.: A Case of Lamblia Intestinalis, Old Dominion J. M. & S. **10**:417 (June) 1910.
5. Emerson: Clinical Diagnosis, Ed. 3, Philadelphia, J. B. Lippincott Co., 1911.
6. Logan, A. H., and Sanford, A. H.: The Significance of Lamblia Intestinalis in Stool Examination, J. Lab. Clin. Med. **2**:618 (June) 1917.
7. McNeil, H. L.: Flagellate Infection of Intestines, Southern M. J. **10**:544 (July) 1917.
8. Smithies, Frank: The Frequency of Protozoic Entercolitis in the Middle West, Am. J. M. Sc. **156**:173 (Aug.) 1918.
9. Hemmeter, J. C.: Clinical Notes on an Intestinal Infection with Giardia Duodenalis, Tr. Am. Gastro-enterological Assn., 1920.
10. Lyon, B. B. V.: Chronic Arthritis with Lambliasis, M. Clinics N. A. **4**:1153 (Jan.) 1921.
11. Simon, S. K.: Lamblia Intestinalis Infestation and Its Treatment, Southern M. J. **15**:458 (June) 1922.
12. McGill, C.: Giardiasis, J. A. M. A. **78**:179 (Jan. 21) 1922.
13. Kofoid, C. A.: Intestinal Protozoan Infections in United States Army Troops, Tr. Am. Gastro-enterological Assn., 1919, p. 262.
14. Maxcy, K. F.: Giardia (Lamblia) Intestinalis Common Protozoan Parasite of Children, Bull. Johns Hopkins Hosp. **32**:166 (May) 1921.
15. Simon, C. E.: Giardia Enterica: a Parasitic Intestinal Flagellate of Man, Am. J. Hygiene **1**:440 (July) 1921.

of the upper intestine. Their nutrition occurs by osmotic processes. In the duodenal contents they frequently present an extremely remarkable picture, the microscopic field literally swarming with these animalcules in a highly active state. When enmeshed in mucus they become motionless, only a few here and there showing sluggish movement. Following the injection of hypertonic solutions into the duodenum, flocculi from the duodenal crypts are extruded, and among the exfoliated duodenal cells small numbers of the parasites are frequently found. I found them in these duodenal flocculi in several instances in which none could be detected in the specimens of the fasting duodenal fluid. When carried from the duodenum into the lower intestine, they become encysted, unless they are hurried along by catharsis or diarrhea. It is easy to overlook the cysts in a routine examination of the feces with the low power lens. They are ellipsoidal and translucent and are slightly smaller than the active organism. Two or four nuclei are usually present. Sometimes they appear structureless. I found that the forms in the duodenal contents as well as those in the stools are well preserved in 10 per cent. solution of formaldehyde. The important structures of the organism can be brought out by the addition of a weak iodin solution to the preparation, and are seen best by the oil immersion magnification.

TRANSMISSION

Authorities differ regarding the transmission of this infection. Since the active parasites die rapidly in the feces after expulsion, transmission between persons must take place by the ingestion of the cysts. Wenyon and O'Connor [16] and Stiles [17] have shown that flies can transfer the cysts. It has also been held, especially by Fantham and Porter,[18] who transmitted the infection from human patients to mice and kittens, that the contamination of food by the fecal discharges of these animals, especially by the "Dachshund rat" in the trenches, is an important factor in the spread of the infection in man. Recently, Simon [19] maintained that specific differences exist between the different forms of *Giardia: Giardia intestinalis* in man, *Giardia muris* in the rat and the mouse, and *Giardia microti* in the meadow mouse. He found that while rats could not be infected with cysts of *Giardia intestinalis* or *Giardia microti,* they could readily be infected with cysts of *Giardia muris.* He therefore concluded that the rat-mouse or meadow-mouse

16. Wenyon, C. M., and O'Connor, F. W.: The Carriage of Cysts of Intestinal Protozoa by House-Flies, J. Roy. Army Med. Corps **28**:522 (May) 1917.

17. Stiles, C. W.: Flies as Carriers of Lamblia Spores, Pub. Health Rep. **28**:2530 (Nov. 28) 1913.

18. Fantham, H. B., and Porter, A.: Giardia Intestinalis, Brit. M. J. **2**:139 (July 29) 1916.

19. Simon, C. E.: Critique of Supposed Rodent Origin of Human Giardiasis, Am. J. Hygiene **2**:406 (July) 1922.

forms of *Giardia* cannot infect man. He believes that the human infection is of human origin. However, it must be pointed out that Fantham and Porter experimented with virulent strains of the organism from human cases of dysentery. They found that the strain from Flanders was more virulent than that from Gallipoli. This difference in virulence might well explain the divergent results obtained by these workers. The organism has also been found in rabbits, dogs, guinea-pigs and sheep.

PATHOGENICITY

The pathogenicity of *Giardia intestinalis* has been the subject of much discussion. The earlier writers believed it to be nonpathogenic. Since the Great War, most authorities hold that while no symptoms are exhibited when the flagellates are few in number, they may become pathogenic when they are present in enormous numbers and cause an enteritis and diarrhea of moderate severity. Thus Porter,[20] in an enumerative study of the cysts of *Giardia intestinalis* in dysenteric feces, estimated that the number of cysts in a bulky infected stool exceeded 14,000,000,000, and in an infected stool of average volume, totaled 324,000,000. It was emphasized that each of these cysts was derived from a flagellate organism provided with a sucking disk whereby it abstracted its nourishment from the intestinal epithelial cells. Furthermore, Wenyon and O'Connor [21] point out that in diarrheal conditions, these cysts frequently occur enmeshed in large quantities of mucus which must be produced by the intestine at the site of the infection. Fantham and Porter [18] found that intestinal lesions can be produced in kittens and mice by the suctorial action of the flagellates.

Those authors that consider *Giardia intestinalis* as nonpathogenic base their opinion on the fact that the parasite may be found in healthy people. In the tropics, they are found in the stools of more than 25 per cent. of apparently healthy persons after a saline purge. However, this same argument can be used to deny the causal relation of *Entamoeba histolytica* to a specific form of dysentery, since Hegner and Payne,[22] in a review of the protozoal infections, record a surprisingly high incidence of healthy carriers of *Entamoeba histolytica*. Stitt [23] takes the extreme view that *Giardia intestinalis* is "responsible for an intractable diarrhoea, an infection only minor in importance to amoebic dysentery."

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20. Porter, A.: An Enumerative Study of the Cysts of Gardia Intestinalis in Human Dysenteric Feces, Lancet **1**:1166 (June 10) 1916.
21. Wenyon, C. M., and O'Connor, F. W.: Lamblia Intestinalis, J. Royal Army Med. Corps **28**:346 (March) 1917.
22. Hegner, R. W., and Payne, G. C.: Surveys of the Intestinal Protozoa of Man, in Health and Disease, Scientific Monthly **12**:47 (Jan.) 1921.
23. Stitt, E. R.: Practical Bacteriology Blood Work and Parasitology, Ed. 2, Philadelphia, P. Blakiston's Son & Co.

Fantham and Porter found 187 cases of pure *Giardia intestinalis* infection among 1,305 soldiers suffering from diarrhea invalided to England from Gallipoli. It is stated by many that the virulence of the infection is greatly reduced in temperate climates. However, Fantham and Porter found that some of their most virulent cases came from Flanders. Woodcock and Penfold,[24] and Kennedy and Rosewarne[25] also report many cases of dysentery in soldiers from the trenches in which only *Giardia intestinalis* was found. Yakimoff,[26] on the firing line in the Caucasus, encountered numerous cases of dysentery in which *Giardia* alone seemed to be responsible. Cade and Hollande,[27] Goiffon and Roux,[28] and Deglos[29] reported cases of diarrhea due apparently to *Giardia*.

There was no history of diarrhea in the nine cases that I encountered. In fact, three of the patients had always been constipated. In none of them could the infection have been considered massive as judged by the number of cysts in the stools. It was difficult to determine the relation of this infection to the clinical symptoms that these patients presented, since other conditions were also present: duodenal ulcer, cholelithiasis, chronic cholecystitis, catarrhal jaundice and anacidity. One case was that of a neurotic girl, 24 years of age, who complained of vague intestinal rumblings and paresthesias. She also presented a sex complex. It was believed that possibly there was some relation between the *Giardia* infection and her abdominal complaints. However, following treatment, with complete eradication of the infection, she still complained bitterly of the same vague abdominal symptoms which could not be dissociated from her psychoneurosis.

While it appeared that *Giardia intestinalis* infection in these cases was merely incidental, the view must be entertained that when another pathologic process is present in the duodenum or gall tract it may be aggravated by the activity of these flagellates.

TREATMENT

The question of treatment is far from settled. The multiplicity of drugs suggested is evidence of their inefficiency as cures. Among the more common remedies suggested are: calomel, turpentine, santonin,

24. Woodcock, H. M., and Penfold, W. J.: Protozoan Infections Occurring at the King George Hospital, Brit. M. J., March 18, 1916, p. 407.
25. Kennedy, A. M., and Rosewarne, D. D.: Lamblia Intestinalis Infections from Gallipoli, Lancet **1**:1163 (June 10) 1916.
26. Yakimoff, V. L., et al.: Chemotherapy of Lambliosis, Russkiy Vrach. **16**:232 (March 11) 1917.
27. Cade, A., and Hollande, A. C.: L'entérite à Giardia intestinalis, Arch. d. mal. de l'app. digestif. **10**:193 (July) 1919.
28. Goiffon, R., and Roux, J. C.: Lamblia enteritis, Arch. d. mal. de l'app.
29. Deglos, F.: Rôle of Lamblia in Intestinal Pathology, Lyon méd. **129**:434 (May 25) 1920.

male fern, beta naphthol, bismuth salicylate and guaiacol carbonate. Transduodenal lavage with solutions of methylene blue or magnesium sulphate is lauded by some. The active flagellate is readily destroyed by these solutions. Cures have occasionally been recorded, but it is doubtful whether they may be looked on as real, since the cases were not rigidly controlled. In untreated cases the ova may be absent from the feces for long periods, and it is unsafe to consider a case as cured unless it is observed for a long time with frequent stool examinations. Thus, Dobell and Low,[30] in examinations of the stools of a patient for 100 consecutive days, found them negative sixty-two days and positive thirty-eight days, with periods as long as ten successive days in which the examinations were negative. The examination of the duodenal contents for the vegetative form gives more reliable data than the search for cysts in the stools. When infection exists, it has been my experience that it is rare not to find the organisms either in the duodenal fluid or in the flocculi from the duodenal crypts following the injection of hypertonic solutions.

It is difficult to eradicate the infection by drugs administered by mouth or introduced by transduodenal lavage, since the flagellates may lodge themselves in the digestive crypts outside the main lumen of the intestine, where they cannot be reached. According to Smithies, they may even lodge in the gallbladder. Such organisms can be attacked best by a drug excreted into these parts from the blood stream. This was done experimentally in 1917, by Yakimoff and others,[26] who eradicated the infection in mice with intravenous injections of arsphenamin. In corroborating this work, Kofoid and others,[31] showed in culture rats, that single injections of arsphenamin freed the animals of the infection only when given in four to eight times the human dose prorated to the body weight of the rat. Smaller doses sometimes reduced the number of cysts, and a single dose, in an amount equivalent to the human dose, had little or no effect. The effect of repeated injections of this last amount was not determined. This was done in 1920 by Carr and Chandler,[32] who reported an apparent cure in a man judged by the disappearance of the cysts from the stools, following three injections of 0.6 gm. at five-day intervals. However, McGill [12] reported the persistence of the infection in a woman following four injections of from 0.3 to 0.6 gm. of neo-arsphenamin at weekly intervals. Goiffon and Roux [28] used arsphenamin with inconstant

30. Dobell, C., and Low, G. C.: A Note on the Treatment of Lamblia Infections, Lancet, Dec. 23, 1916, p. 1053.

31. Kofoid, C. A., et al.: On the Treatment of Giardiosis in Rats with Arsenobenzol, J. Med. Res. **34**:293 (Jan.) 1919.

32. Carr, E. I., and Chandler, W. L.: Successful Treatment of Giardiasis in Man with Neoarsphenamin, J. A. M. A. **74**:1444 (May 22) 1920.

results. Recently, Simon [11] reported the use of repeated injections of arsphenamin in several cases followed by the disappearance of cysts from the stools. However, insufficient data are given regarding the frequency of the examinations, and the duration of observation to prove his patients cured.

Of my series, three patients, whose cases are summarized below, submitted to treatment. They were three women of approximately the same weight, and they received the usual doses of arsphenamin. Only in the first case was a cure effected. This case differed from the others in that a duodenal lavage with magnesium sulphate, for the purpose of recovering the parasite, was given between the intravenous injections. Prior to the arsphenamin treatment repeated lavage with magnesium sulphate had failed to eliminate the organism. It was believed at first that the disappearance of the parasite in this case was due to the action of the neoarsphenamin alone; therefore no duodenal lavage was given in the two subsequent cases. However, in these two cases the infection reappeared. It is possible that those organisms that are enmeshed in mucus, as in the duodenal flocculi, are protected against the action of the arsphenamin in the doses used. Duodenal lavage with the hypertonic solution of magnesium sulphate can rid the host of such forms.

AUTHOR'S CASES

Case 1.—Miss L. G., aged 21, weight 102 pounds (46.26 kg.). Diagnosis: Neurosis.

Treatment.—May 9, 1922, 0.45 gm. neo-arsphenamin.
May 12, 1922, Duodenal lavage, 90 c.c. of 30 per cent. of magnesium sulphate (No *Giardia* found in the duodenal contents).
May 13, 1922, 0.45 gm. neo-arsphenamin.
May 14, 1922, Duodenal lavage, 90 c.c. of 30 per cent. of magnesium sulphate (No *Giardia* found in the duodenal contents).
May 16, 1922, 0.45 gm. neo-arsphenamin.
May 17, 1922, Duodenal lavage, 90 c.c. of 30 per cent. of magnesium sulphate (No *Giardia* found in the duodenal contents).

Result.—Fourteen examinations of the duodenal contents, up to six months since the last treatment, were negative for *Giardia.*

Case 2.—Mrs. F. S., aged 31, weight 112 pounds (50.8 kg.). Diagnosis: Chronic cholecystitis.

Treatment.—June 6, 1922, 0.3 gm. of arsphenamin.
June 10, 1922, 0.3 gm. of arsphenamin (Had arsphenamin reaction).
June 15, 1922, 0.2 gm. of arsphenamin (Had arsphenamin reaction).

Result.—Aug. 26, 1922, duodenal examination: *Giardia* present. Stool negative for cysts.

Case 3.—Mrs. N. D., aged 52, weight 118 pounds (8.1 kg.). Diagnosis: Anacidity.

Treatment.—July 1, 1922, 0.45 gm. neo-arsphenamin.
July 6, 1922, 0.45 gm. neo-arsphenamin.
July 11, 1922, 0.45 gm. neo-arsphenamin.

Result.—July 30, 1922, duodenal examination: *Giardia* present. Stool, vegetative forms and cysts present.

SUMMARY

1. *Giardia intestinalis* infection is not rare. In the routine examination of the duodenal contents in 170 residents of New York City, nine cases of this infection were found.

2. While *Giardia intestinalis* is probably capable of producing a diarrhea of moderate severity, no symptoms attributable to this infection could be definitely established in the cases presented.

3. Three patients were treated with three arsphenamin injections in the usual doses at three to five-day intervals. This procedure was not successful in eradicating the infection in two cases. One case in which the injections were alternated with duodenal lavage with magnesium sulphate the patient remained free from the infection during fourteen examinations of the duodenal contents over a period of six months.

GONORRHEAL MYELITIS *

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The few cases reported in the literature of spinal cord involvement following a gonorrheal urethritis, and presumably due to a metastatic gonococcal infection or a gonotoxin, sufficiently support the possibility of such an occurrence, and it is the custom of textbook authors to devote a few lines to a general consideration of this subject. A careful search through the literature failed to uncover any reported cases or review of cases of this condition by investigators in this country, and the few scattered reports by others are contained in foreign journals. Because of the rarity of the condition and the fact that, so far as we have been able to determine, no review of reported cases has ever been made, we have compiled all available reports, and submit two such instances of our own.

Numerous records of gonorrheal meningitis are available, and while there has been considerable confusion and much discussion as to the diagnosis because of the similarity in characteristics of the gonococcus and the meningococcus, sufficiently controlled laboratory work has shown that the gonococcus may play the causative rôle in a meningitic infection. Cases reported establishing this fact both clinically and in the laboratory are those of Wooten,[1] Henderson and Ritchie,[2] Blind and Ricord,[3] Boivin,[4] Lindenfeld,[5] Malleterre,[6] Rombach,[7] Prochaska,[8] Chavrier and Fevrier,[9] and Gordon.[10] However, we have attempted to limit this paper to a consideration of cases in which there have been definite spinal cord changes without necessarily showing evidence of meningeal involvement.

Stanley,[11] in 1833, was the first to describe paraplegia occurring in the course of gonorrhea, calling it "urinary paraplegia," and believing

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1. Wooten, J. S.: Acute Gonorrheal Meningitis, J. A. M. A. **32**:170, 1899.
2. Henderson and Ritchie: Rev. Neurol. & Psychol. **7**:75, 1909.
3. Blind and Ricord: Paris méd. **21**:312, 1917.
4. Boivin: Bull. Soc. méd. d. hôp. de Paris **43**:1024, 1919.
5. Lindenfeld: Med. Klin. **18**:176, 1922.
6. Malleterre: New York M. J. **103**:1024, 1916.
7. Rombach: Nederlansch Tijdschr. v. Geneesk. **51**:1262, 1907.
8. Prochaska: Deutsch. Arch. f. klin. Med. **83**:184, 1905.
9. Chavrier and Fevrier, quoted by O'Connor: Arch. de méd., Paris, 1888.
10. Gordon: Diseases of the Nervous System, 1917, pp. 465 and 586.
11. Stanley: Med. Chir. Tr. **18**:260, 1833.

it to be of reflex origin due to sensitive nerves transmitting a morbid impression to the cord, which was thence reflected to the muscles. Gull,[12] in 1856, did not accept Stanley's views, and showed that the cord was actually altered. Hayem and Parmentier[13] drew attention to the frequency of gonorrheal arthritis with spinal phenomena. They believed that the nerve roots suffered an inflammatory reaction and that there must be a meningomyelitis. Charcot[14] expressed the opinion that such cases were only indirectly due to gonorrhea; that the spinal affection was arthritic in origin, and that the existence of arthritis was an essential preliminary. Nearly 55 per cent. of the reported cases exhibiting no joint involvement have been decisive against this theory. Dufour[15] asserted that gonorrhea opens the door to secondary infections which bring about myelitis. The possibility of true gonorrheal metastasis to the spinal cord is conceded by Raymond and Cestan,[16] while Moltschanoff[17] seeks to demonstrate the effect of gonotoxin on the spinal ganglions of the nervous system. Whether the changes produced in the spinal cord are due to a gonotoxin, to the action of the gonococci themselves or to secondary invaders, has never been definitely established. Although neither bacteriologic examination of the spinal fluid nor sections of the cord have yielded gonococci in any of the examinations, we are inclined to believe that the changes must be due to the direct action of the gonococci themselves through metastasis to the cord. Were toxins alone to blame, it is reasonable to suppose that in the many severe gonorrheal infections seen, there would be more cases of spinal cord involvement; and again, nearly 45 per cent. of instances of myelitis of supposed gonorrheal origin show also some complication of an evident gonorrheal metastatic nature, for example, arthritis. However, it may be, as O'Connor[18] states, that gonorrheal complications cannot be rigidly attributed to the gonococcus alone, but, as in every other infective disease, every complication has a complex etiology.

In a careful survey of the literature for reported cases of myelitis following gonorrheal urethritis, we were able to find twenty-nine instances which may be accepted either from a clinical standpoint or from the anatomic findings in conjunction with the history. Such records are those of Stanley,[11] two cases by Gull,[12] four cases by Hayem and Parmentier,[13] Charcot,[14] Dufour,[15] two reports by O'Connor,[18]

12. Gull: Med. Chir. Tr. **39**:195, 1856.
13. Hayem and Parmentier: Rev. de méd. **8**:433, 1888.
14. Charcot: Leçons sur les mal. du syst. nerv. **1**:3, 1880.
15. Dufour: Thèse de Paris, 1889.
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17. Moltschanoff: Arch. Russ. de Path. **7**, 1899.
18. O'Connor: Quart. J. M. **15**:69, 1921.

Eulenberg,[19] four instances by Delamare,[20] Peter,[21] Tixier,[22] two cases by Spillmann and Haushalter,[23] von Leyden,[24] Speranski,[25] Pissavy and Stévenon,[26] Olmer,[27] Rogalsky,[28] Luys,[29] Gowers,[30] and Raynaud's[31] report of one case of Moreau's and one of Gemy's. To these we wish to add the reports of two cases of our own.

REPORT OF CASES

Case 1.—*History.*—Mr. J. S. B., aged 23, single, Swedish, a salesman, entered Cook County Hospital on March 20, 1922, complaining of inability to walk or move his legs, inability to urinate and discharge from the penis. He said that about two weeks previously he had first noticed the urethral discharge coming on seven days after exposure in intercourse. He had endeavored to treat himself with various hand injections, and until four days ago had experienced no unusual symptoms. At this time he first noticed a feeling of weakness in both lower limbs. However, he remained up and about and paid little attention to the condition. The following morning the weakness was more marked, and during the course of the day he experienced several chills lasting ten or fifteen minutes, followed by sweating and fever. The weakness became progressively worse so that by evening he was confined to his bed. The following day he was able to be up on his feet for short periods, but began experiencing some difficulty in voiding urine, and by evening this partial retention became complete so that it was necessary to catheterize him, a condition which had persisted until the time of his entrance into the hospital. The following day, which preceded his coming to the hospital, he was unable to stand or walk, or even to move his lower limbs—a paralysis which has remained unchanged.

The past history was negative, except for the usual childhood diseases and the removal of the tonsils. The venereal history disclosed three previous gonorrheal infections. The family history was essentially negative.

Physical Examination.—This disclosed a well nourished male adult who, beyond his inability to walk, did not appear acutely ill. Regional examination proved to be negative or normal in all essentials, with the exception of the genitals and the extremities. A profuse purulent discharge exuded from the urethra; the bladder extended about three fingerbreadths above the symphysis by percussion; the prostate was only slightly enlarged and not excessively tender, although giving a false impression of enlargement because of the distended bladder. The testicles were both present in the scrotum, and with their epididymidides presented no abnormal findings. The extremities exhibited a flaccid paralysis, although this was not complete, the patient being able to move his toes slightly, and there was some response to the effort to bend the right knee. Complete anesthesia both anteriorly and posteriorly up to the level of the anterior spines of the ilium was present. On

19. Eulenberg: Deutsch. med. Wchnschr. **36**:686, 1900.
20. Delamare: Gaz. d. hôp. de Paris **76**:549, 1901.
21. Peter: Gaz. hebd. de méd. **3**:764, 1866.
22. Tixier: Thèse de Paris, 1866.
23. Spillmann and Haushalter: Rev. de méd. **11**:651, 1891.
24. Von Leyden: Ztschr. f. klin. Med. **21**:607, 1892.
25. Speranski: Med. Oboz. Moskow. **39**:770, 1893.
26. Pissavy and Stévenon: Bull. Soc. méd. d. hôp. de Paris **24**:919, 1907.
27. Olmer: Rev. neurol. **18**:115, 1910.
28. Rogalsky: Tunisie méd., Oct., 1912, p. 313.
29. Luys: Gonorrhea and Its Complications, London, 1913, p. 226.
30. Gowers: Med. Press and Circ., London **89**:249, 1910.
31. Raynaud: Rev. de méd. **12**:183, 1892.

the admission of the patient, the reflexes were somewhat exaggerated; they soon became variable, and at the end of a week were abolished. Incontinence both of urine and feces was present from the time the patient was first seen, the urinary incontinence being of the paradoxic type. No evidence of pathologic changes in the spine could be made out.

Laboratory Findings.—The findings were: red blood cell count, 4,960,000; white blood cell count, 11,400; differential white blood cell count: polymorphonuclears, 71 per cent.; small lymphocytes, 12 per cent.; large lymphocytes, 11 per cent.; eosinophils, 1 per cent; transitionals, 5 per cent. Urine examination of a catheterized specimen showed a small amount of albumin with a large number of pus cells and a few red blood cells. Smears from the urethra discharge disclosed a large number of gram-negative intracellular and extracellular diplococci, in typical gonococcal arrangement, which were recovered as such on culturing. Smears from the expressed prostatic and seminal secretions likewise showed similar organisms with a large number of pus cells. Spinal fluid examination revealed a clear fluid under no increased pressure, no increase in the cell count and no globulin with the Ross-Jones, Nonne and Pandy tests. Direct smears of the spinal fluid sediment revealed no organisms. Cultures in broth and on blood agar and Löffler's serum, as well as on dibasic sodium phosphate ascitic agar, remained sterile up to the third day. In sugar broth, smears revealed a gram-positive coccus, while agar cultures from this broth remained sterile, probably a contamination. Roentgen-ray examination of the dorsolumbar spine failed to show any pathologic condition, while a tendency toward an osteo-arthritis was noted in the sacro-iliac articulations. The blood Wassermann test was negative, as was that of the spinal fluid. The Lange reading on the spinal fluid was 0001110000. Blood chemistry determination gave the following figures: total nitrogen, 2.750; nonprotein nitrogen, 28.00; urea nitrogen, 38.29; urea, 81.94; uric acid, 3.40 and creatinin, 1.67. A blood culture remained sterile after forty-eight hours.

Treatment and Course.—Little elevation of temperature occurred, and the condition of the patient generally was good. Urination by overflow was established, and urinary antiseptics given. His condition remained stationary until fourteen days after admission, when he developed a right epididymitis. Intravenous injection of a polyvalent gonococcus vaccine was given and followed by some relief and diminution of the swelling of the affected epididymis. On the fifteenth day there was evidence of a beginning decubitus ulcer despite the careful measures taken to prevent this. The patient was placed on his abdomen on a Bradford frame, and all friction points carefully padded. However, the sacral ulcer continued to form, and finally exposed the sacrum for an area of about 12 cm. in diameter. There was marked edema of the scrotum and penis; his condition became progressively worse and was accompanied by a universal toxic erythema. Death occurred on April 29, 1922, thirty-nine days after admission to the hospital and forty-three after the onset of the symptoms.

Measures undertaken to secure a necropsy were unavailing, except for an examination of the brain. This proved negative both grossly and histologically, except for a moderate amount of edema.

Case 2.—*History.*—J. M., aged 26, single, an American, a chauffeur, entered Cook County Hospital on Jan. 28, 1920, complaining of inability to urinate, difficulty in walking, and numbness and tingling of the lower extremities. He states that until the day preceding his entrance into the hospital he had been perfectly well, except for a chronic discharge from the penis, which had its onset in March, 1919, and, following a temporary respite, had recurred in October, 1919, to persist up to the present time. Two days previous to his admission he first experienced some difficulty in urinating, chiefly marked by straining and some dribbling. The following day he was unable to void, was nauseated, vomited, had chills and some fever, and first noticed a tingling and numbness in his lower extremities, which, however, did not prevent his getting

about. On the morning of his admission, however, he said that his limbs were very weak, and in walking he was forced to drag his legs and to spread them far apart; then, with considerable effort, he was able to move about. With the exception of diphtheria in 1914, his past illnesses were limited to the usual childhood diseases. The venereal history dated from March, 1919, when the initial gonorrhea occurred. He denied ever having had a chancre. The family history was unimportant.

Physical Examination.—This disclosed a white adult male, well nourished and developed, and apparently not acutely ill. The bladder on percussion was found four fingerbreadths above the symphysis. The urethra discharged a heavy yellow pus, while the testicles and epididymidides were normal. The prostate was slightly enlarged and tender, although not markedly so. The lower extremities were cyanotic and cold, and exhibited a marked loss of motor and sensory power. However, there was not a complete paralysis, as the patient was able to bend both knees slightly, as well as flex and extend the toes, and motion from the hip joint was not entirely gone. The reflexes were exaggerated, with slight ankle clonus and absent Babinski sign. There was a noticeable loss of sensation, especially along the anterior surfaces, extending as high as the umbilicus, where a hyperesthetic zone was found. Cystoscopic examination was made, a 24 F. catheterizing cystoscope passing without obstruction. The bladder was tolerant to fluid and instrumentation, and 28 ounces (800 c.c.) of retained urine was secured. Marked atony of the bladder existed, the entire floor sagging, while a moderate silky trabeculation was present. The ureteric orifices were seen to be greatly dilated, and no rhythmic contractions or efflux was present. The entire cystoscopic picture was that seen in typical cases of cord lesion bladders. Both kidneys were catheterized and specimens secured for cultural study.

Laboratory Findings.—Red blood cell count was 5,100,000; white blood cell count, 9,800. Urine examination revealed albumin in small amounts with many pus cells and a few red blood cells. Catheterized kidney specimens revealed normal findings for both sides, chemically, culturally and microscopically. Smears from the urethral discharge showed many pus cells and a large number of gram-negative intracellular and extracellular diplococci. The blood Wassermann test was negative, as was that on the spinal fluid. Examination of the spinal fluid revealed a clear fluid under slightly increased pressure, with negative globulin reactions and no increase in the cell count. The Lange curve read 0011110000. Direct smears from the sediment revealed no organisms, and cultures on blood agar and Löffler's serum, as well as in broth, remained sterile after forty-eight hours. A radiogram of the dorsolumbar region failed to reveal any spinal pathologic condition.

Course.—Incontinence of urine and feces persisted until twelve days after admission, when he slowly began to recover the power of voluntary urination and defecation. This was followed by a more rapid improvement in the motor function of the lower extremities, so that twenty-five days after admission and twenty-seven days after the onset of the symptoms, he was discharged from the hospital. While at this time he was still somewhat weak, he was able to move about with only slight dragging of the legs and straddling. He was able to control the act of urination without straining or dribbling, and to all obvious symptoms was well on the way to entire recovery. This patient was seen again three years later, and at this time exhibited no symptoms of his former difficulty and was apparently in perfect health.

COMMENT

While it has been impossible to prove definitely the gonococcus as the etiologic factor in these cases from the standpoint of laboratory findings, it must be conceded that in two persons who were in perfect

health, with the exception of an acute and a chronic gonorrhea, the evidence from a clinical standpoint in favor of this is extremely strong, and certainly these two cases approximate in all their aspects those reported in the literature as gonorrheal myelitis.

A review of the reported case histories found in the literature shows the occurrence of this condition in twenty-six males and three females. The age incidence was between 15 and 40 years, with the greatest number occurring between the ages of 18 and 30. The gonorrheal urethritis was determined as acute in one case, chronic in twenty-three instances and not given in five. The number of infections ranged from one to "numerous," the largest number given being three. The duration of the infection at the time the patient presented the symptoms of myelitis ranged from "recent" to twelve years, the majority occurring between two months and a year after infection. Of the twenty-nine cases, fourteen patients, or nearly 45 per cent., suffered from a gonorrheal complication, of which twelve were arthritic in nature chiefly involving the knees; there was one case of endocarditis, and one of iritis which were considered to be of gonorrheal origin. The onset where mentioned was sudden in all of the cases. Twenty-two of the cases began with pain in the back and along the thighs, to be shortly followed by the nervous manifestations; in two, the mode of onset was without premonitory symptoms. The sphincters were not involved in seven cases, while sensation was undisturbed in two. The presence of a decubitus ulcer was mentioned in four instances. All of the patients showed motor loss in greater or less degree, and the reflexes were correspondingly involved. Of the twenty-nine patients, eight, or about 24 per cent., died, of which number six went to necropsy, with the resulting anatomic diagnosis of myelitis. The length of time elapsing between the onset of the paralysis and death varied from sixteen hours to four months. In two instances only were bulbar phenomena mentioned. Complete recovery occurred in ten cases, or 34 per cent.; recovery with one recurrence took place in one case, and recovery with four recurrences in one case. One patient was still in the hospital at the time of the report, and three left the hospital before recovery, while in four instances the outcome was not mentioned.

Delamare has divided these cases into acute, subacute and chronic manifestations, while Pissavy and Stévenon think that a good dividing line between slight and severe forms is struck by the presence or absence of sphincter troubles. All of the cases exhibiting acute onsets and symptoms died, and accepting Delamare's division, we have found eight of the acute type, three subacute and eighteen of the chronic form of myelitis.

The pathologic changes, so far as the spinal cord is concerned, depend on the stage of degeneration and the severity of the inflam-

matory process. There is usually flattening of the cord at the seat of the lesion, and at this point it is much softer than the remainder. On section, the distinction between the gray and white matter is lost or indistinct. The microscope will show swelling and distortion of the nerve fibers, beading of the axis cylinders, abundant myelin droplets and sometimes corpora amylacea. Swelling of the ganglion cells with granular and vacuolated protoplasm, distended veins, leukocytic infiltration and degenerated nerve fibers are seen. Following the acute stage, the so-called red or inflammatory softening is succeeded by fatty degeneration, and a change in color to yellow and finally white as sclerosis sets in.

The symptoms are those common to myelitis from any cause. The onset is usually sudden, and the symptoms not long in manifesting themselves. There may be pain in the legs or back, or a girdle sensation, together with chills and sometimes convulsions. Motor functions are rapidly lost, and following hyperesthesia sensation is disturbed. Early the reflexes are exaggerated, later becoming variable and finally abolished. The rectal and bladder sphincters are paralyzed, and there is usually wasting of the muscles and trophic disturbances; while the temperature of the affected parts is lowered, and decubitus ulcers make their appearance. The myelitis may be of an ascending type, with cervical paraplegia, bulbar symptoms and death. In the acute cases the symptoms become aggravated, the pulse rapid, the tongue dry and delerium sets in to be followed by coma and death. Patients with subacute and chronic cases usually recover, although the paraplegia may persist for some time, and occasionally there are recurrences, while trophic changes are not marked, and sphincter disturbances may be absent.

The diagnosis in these cases must be made chiefly by exclusion, and for this purpose a comprehensive history, a thorough physical examination with special attention to the neurologic findings and reliable laboratory determinations must be secured. The rapid and progressive motor paralysis, the relaxation of the sphincters, corresponding sensory disturbances or anesthesia surmounted by a band of hyperesthesia, the muscular atrophy, exaggerated reflexes below the site of the lesion and the loss of faradic response in the muscles together with trophic changes and decubitus ulcers determine the question as to the presence of a myelitis. The origin must be determined from the history, the evidence of traumatism, acute infectious diseases, syphilis, septicemia and spinal cord tumors. Among the conditions to be differentiated are chiefly poliomyelitis, meningitis, multiple neuritis, Landry's paralysis and hysteria. In poliomyelitis, the motor loss is usually of the monoplegic type, and sensory changes are generally absent. In meningitis there is retention of motor power and reflexes. In multiple neuritis

the onset is slow; all extremities are involved, particularly the extensors, while the bladder and rectum are rarely affected, and trophic changes are not seen. In Landry's paralysis, there is a steady advance of the paraplegia from the lower extremities upward, with undisturbed sensation, retention of bladder and rectal control and reflexes. In hysteria, reflexes are not disturbed, trophic changes are not present, and hysterical stigmas are obtainable, while the sensory disturbance has a characteristic outline. With the exclusion of all other possible causative agents, the basis for the assumption that the gonococcus, in a patient suffering from a gonorrheal infection, is the causative factor producing the myelitis is perfectly logical.

The prognosis is, of course, dependent on the changes present in the individual case, but in general it is to be considered grave as to life and certainly as to complete recovery.

The treatment in these cases is chiefly symptomatic, while the attempt is made to prevent the development of complications. The wisdom of attempting to eradicate the focus in the urethra by active measures directed to the posterior urethra is debatable, and in our opinion efforts directed toward the building up of the general body resistance will prove more effective. The danger of an ascending urinary infection is great, and it has been our experience in dealing with myelitis from any cause that the establishment of urination by overflow is not desirable. By means of a small suprapubic puncture with the insertion of a catheter for drainage through a cannula, as in dealing with an empyema by the closed method, it is possible to secure adequate drainage and to carry out systematic lavage of the bladder. The use of a Bradford frame, or a water or air bed, with careful padding of all pressure points is essential in the avoidance of dystrophic bedsores. The nutrition of the muscles should be maintained by intelligent massage or electrotherapeutic measures from the beginning, and the position of the limbs should be frequently changed. The general physical condition should be watched carefully, and beyond the usual symptomatic measures, the treatment resolves itself to the prevention of complications.

MALIGNANT LYMPHOMA (HODGKIN'S DISEASE)

A RADIOGRAPHIC STUDY

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This investigation of Hodgkin's disease is based on the study of forty cases examined radiographically at the Massachusetts General Hospital and seven cases of which necropsies were made.

Hodgkin's disease is often confused in diagnosis with other conditions, especially tuberculosis, and patients are thus denied the benefits of roentgen-ray therapy. One patient in our series was sent to Arizona for tuberculosis, only to find out later that the long trip was to no purpose.

The chest is the most fruitful field for radiographic examination in this disease because the low density of the lungs allows masses of lymphomatous tissue to show up well, and because the chest is often involved—seven out of twenty-two cases which came to necropsy.

The radiographic appearance is characteristic enough to be of great value in the differentiation from other forms of malignancy and tuberculosis.

REVIEW OF THE LITERATURE

References to the radiographic diagnosis of Hodgkin's disease are to be found chiefly in articles dealing with the radiographic diagnosis of mediastinal tumors and other intrathoracic conditions. The only article dealing primarily with the radiographic findings in Hodgkin's disease which I was able to find is one by Wessler and Greene,[1] to be discussed later. Since I shall discuss the relation between Hodgkin's disease and lymphosarcoma, quotations will be made from the literature on these two subjects.

Thomas [2] says that "lymphosarcoma is the most frequent mediastinal growth. There may be observed distinct indications of irregular involvement of the adjacent tissues. In Hodgkin's disease the involved glands are apt to be quite large and discrete."

Walton [3] sees in lymphosarcoma "irregular growths with sharply defined outlines often somewhat nodular in shape and extending far beyond the limits of the mediastinum. These tumors do not tend to

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1. Wessler, H., and Greene, C. M.: Intra-thoracic Hodgkin's Disease. Its Roentgen Diagnosis, J. A. M. A. **74**:445 (Feb. 14) 1920.
2. Thomas, George F.: The Roentgen Diagnosis of Lesions in the Region of the Mediastinum, Am. J. Roentgenol. **1**:133, 1914.
3. Walton, H. J.: Roentgenological Examination of the Mediastinum. Am. J. Roentgenol. **5**:181, 1918.

invade or infiltrate the surrounding tissues but often cause marked displacement of the viscera. . . . In Hodgkin's disease the lungs may be infiltrated giving the impression of a tuberculous process. In roentgenograms they are represented by shadows which are usually oval or elongated and appear either singly or massed together."

According to Kahn,[4] "lymphosarcoma usually manifests itself as a large single shadow and may occupy the greater part of the chest. . . . Hodgkin's disease roentgenologically resembles somewhat lymphosarcoma; indeed the mediastinal shadows of these two diseases cannot be absolutely differentiated."

Childs[5] asserts that "lymphosarcoma starts in the mediastinum and is apt to increase rapidly in size and involve the lung or pleura or both. . . . Hodgkin's disease is generally shown by a paratracheal, dense shadow projecting beyond the mediastinum with a border either irregular in outline or circumscribed and clearly defined, which extends over a considerable part of the median shadow. These masses may attain to a large size, projecting beyond the mid-clavicular nipple line, and extend the entire length of the median shadow. Occasionally only a unilateral mass projects at the level of the hilus, circumscribed by a border similar to that above described."

In the work of Lemon and Doyle,[6] "Hodgkin's disease is suspected when the roentgenogram reveals a bilateral feathery shadow passing outward from each hilus." And as to the value of radiographic evidence: "A pathologic diagnosis hardly should be expected from the roentgenographic findings but in eight cases (out of twenty-six) a positive opinion was reached."

RADIOGRAPHIC APPEARANCES IN HODGKIN'S DISEASE AS INTERPRETED FROM THE PATHOLOGY

To best interpret the radiographic appearances of Hodgkin's disease it is necessary to have a clear picture of the gross pathology in mind as the plate is being examined.[7]

The enlarging glands form more or less lobulated tumor masses, the lobules being rather smooth and discrete, varying from the size of a pea to that of a hen's egg or larger. Since the glands are fairly

4. Kahn, M.: X-Ray Studies of Mediastinal Shadows with Special Reference to Dermoid Cyst, J. Radiol. **3**:45, 1922.

5. Childs, S. B.: New Growths Within the Chest, Am. J. Roentgenol. **10**: 3-175, 1923.

6. Lemon, W. S., and Doyle, J. B.: Clinical Observations on Hodgkin's Disease with Special Reference to Mediastinal Involvement, Am. J. M. Sc. **162**: 525, 1921.

7. Longcope, W. T., and McAlpin, K. R.: Hodgkin's Disease, Oxford System **4**:1, 1921. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1920, p. 853.

dense and homogeneous the radiographic appearance is somewhat like a silhouette of a lobulated mass extending into the lung field.

The glands vary considerably in density because fibrosis in them is progressive. The result is that in early cases the radiographic shadows are less dense than in older cases, and sometimes the outlines of several lobules can be distinctly seen (Figs. 2 and 14). In older cases, the lobulation may be lost and the appearance of a large tumor mass may be seen in the mediastinum (Figs. 3 and 4). Matting of the nodes together by fibrosis occurs after secondary infection or roentgen-ray treatment.[8] On account of this fibrosis, the large tumor masses of

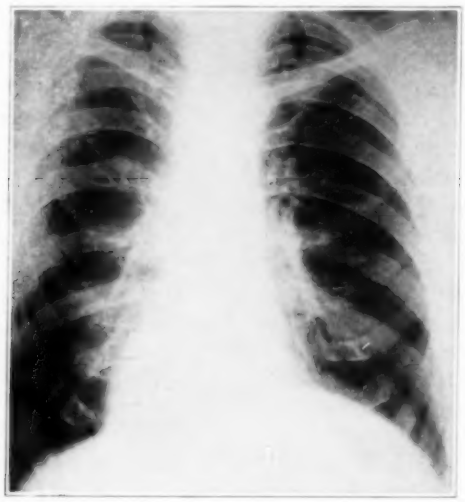

Fig. 1.—Normal chest; some evidence of peribronchial thickening, but within normal limits.

Hodgkin's disease seldom have the regular outlines of an aneurysm or mediastinal carcinoma.

Occasionally in late or acute cases, instead of expanding evenly, the lymphomatous masses infiltrate the lung tissue,[9] extending out from the hilus and giving somewhat the appearance of the peribronchial thickening and diffuse clouding of the lung fields seen in bronchopneumonia (Figs. 6, 7, 8 and 9).

Two of the seven cases that came to necropsy had lymphomatous infiltration of the lungs (Figs. 8 and 9).

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8. Footnote 6. Longcope: Footnote 7.
9. Footnotes 1 and 3.

Seven of our forty patients had pleural effusions, five in the left, and one in both pleural cavities (Figs. 10 and 11). Lemon and Doyle [6] found fluid in four out of twenty-six cases.

TYPES OF INTRATHORACIC INVOLVEMENT IN HODGKIN'S DISEASE ACCORDING TO RADIOGRAPHIC FINDINGS

Wessler and Greene,[1] from a study of twenty-five cases radiographically, have divided intrathoracic involvement in Hodgkin's disease into four groups.

Group 1.—Mediastinal Tumor: These are masses extending out from the mediastinum into the lungs—eight of the twenty-five cases. Twenty-two of our forty cases showed this condition (Figs. 3, 4, 12 and 13).

Fig. 2.—Hodgkin's disease. Typical nodular shadows at right hilus; slight upper mediastinal involvement. A man, aged 26, for four months had severe pain in the hips, legs and back. He had a wheezy cough at night, but there was no sputum. His appetite was poor; he lost 15 pounds (6.8 kg.) in six months. There had been no exposure to tuberculosis, and there was none in his family. Physical examination revealed small discrete nodes in the neck, dulness over the upper four dorsal vertebrae, supracardiac dulness, 9 cm. Blood examination revealed a white blood count of from 19,000 to 33,000; polymorphonuclears, from 80 to 92 per cent.; lymphocytes, from 2 to 11 per cent.; large mononuclears, from 6 to 10 per cent.; eosinophils, from 1 to 2 per cent. The red blood count was 3,900,000, and hemoglobin from 50 to 80 per cent. In the evening, the temperature rose to from 102 to 103 F., with morning remissions lasting twenty days, ten days after roentgen-ray treatment. The biopsy report was: malignant lymphoma.

Group 2.—Infiltrative Type; four cases. "Borders of the infiltrating mass are indistinct and irregular. It may be a diffuse transformation of

intra-pulmonary lymphatic tissue into granuloma" (Wessler and Greene). Eleven of our cases showed this condition (Figs. 6, 7, 8 and 9).

This may represent the condition which some classify as lymphosarcoma.[10]

Group 3.—Isolated Nodules or Metastases in the Lung. Four cases. "Circular or oval shadows of moderate density, usually one to several centimeters in diameter. Probably these shadows are due to the development of lymphomatous foci in pre-existing lymphatic tissue (Wessler and Greene.)

None of our series showed this condition clearly on the radiograph although one of the seven cases that came to necropsy did show masses of lymphomatous tissue 1 to 3 cm. in diameter in the upper lobes. (Fig. 8).

One possible source of error in interpreting oval or circular shadows a few centimeters in diameter is that they may represent fibrotic areas of some old pathologic process. For instance, two of our seven at necropsy showed foci of obsolete tuberculosis in the lungs.

Group 4.—Discrete Nodes at the Roots of the Lungs. Seventeen cases. "This is the most common type. The shadows often extend for a considerable distance from the roots of the lungs and retain a definite outline. The shadows are rather faint, differing in this respect from other forms of malignancy and tuberculosis." (Wessler and Greene.)

Thirty-three of our forty cases showed this condition radiographically, being by far the most common type of involvement in our series as well as in theirs (Figs. 2, 14 and 15).

The faintness of the shadows mentioned by Wessler and Greene may be due to young lesions before much fibrosis has taken place in the nodes. It would seem that homogeneity of the shadows is a more important factor in their differentiation from tuberculosis. In that disease, the shadows are of irregular density showing some very dense spots due to calcification.

In fourteen of their twenty-five cases they noted an involvement of the right paratracheal nodes; they considered this a factor of importance in differentiating Hodgkin's disease from tuberculosis and other forms of malignancy, except in the tuberculosis of children in which these glands are often affected.

Seventeen of our forty cases showed this condition, or at least showed a widening of the upper mediastinal shadows (Figs. 2, 12 and 13).

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10. Footnotes 2 and 5.

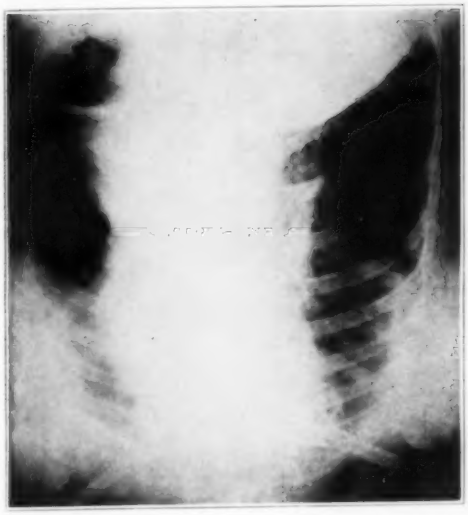

Fig. 3.—Late case of Hodgkin's disease, with upper mediastinal involvement. Two years ago, a man, aged 35, noticed a nodular ridge above the right clavicle which grew slowly. There were no symptoms until nine months before, when slight dyspnea and dysphagia began, gradually increasing. Physical examination revealed large nodes in the neck and axillae, hard, painless, discrete and freely movable. The chest findings were: dulness, bronchial breathing and râles over the upper halves of both chests. This was a typical case of Hodgkin's disease, and roentgen-ray treatment gave marked relief.

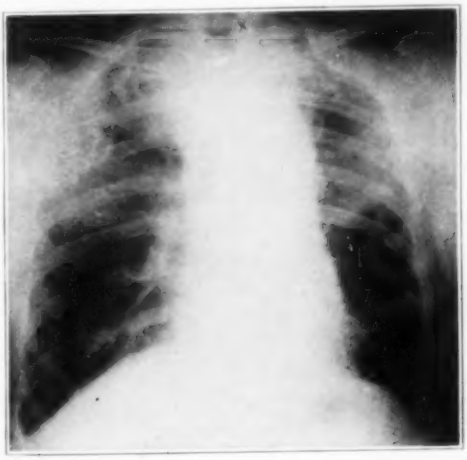

Fig. 4.—Same case as in Figure 3 after six months of roentgen-ray treatment.

Fig. 5.—Carcinoma of the mediastinum. A man, aged 53, had dyspnea and dysphagia, with slight dulness at the apexes of the lungs and at the left base. Fluoroscopic examination revealed a nonpulsating mass behind the heart, trachea and esophagus, and slight erosion of the bodies of the vertebrae. The roentgenogram showed a large, clearly outlined mass so dense that its borders were seen through the heart. The diagnosis was mediastinal carcinoma.

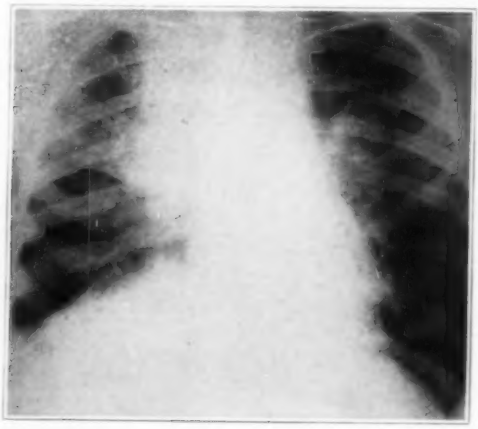

Fig. 6. Hodgkin's disease with infiltration of the lung. There were enlarged nodes in the neck three months before this roentgenogram was taken, but the lungs were negative at that time.

Fig. 7. Same case as in Figure 6. The lymphoma is reduced in size and density as the result of five months of roentgen-ray treatment.

Fig. 8.—Hodgkin's disease with nodules of lymphomatous tissue in the lungs at necropsy. There was a lymphoma of the bronchial glands, with masses of lymphomatous tissue from 1 to 3 cm. in diameter in the upper lobes. The roentgenogram indicates a diffuse peribronchial process involving chiefly the hilums and upper lobes. The small, indistinct shadows in the lung fields may indicate infiltrating masses of lymphoma or they may indicate fibrotic areas of an old inflammatory process.

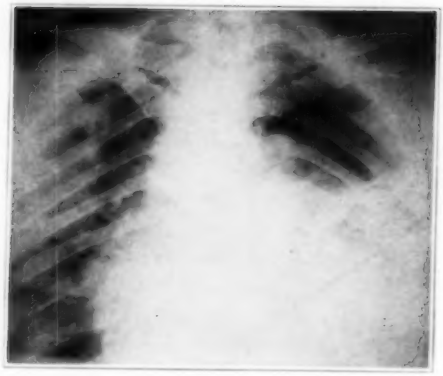

Fig. 9.—Hodgkin's disease, rapidly fatal. Necropsy revealed lymphoma of the mediastinal and bronchial lymph nodes infiltrating the lungs and involving the pleura. This might have been a case of lymphosarcoma.

Fig. 10.—Hodgkin's disease with fluid. A man, aged 39, had a cold and a cough nine months before this roentgenogram was taken. The loss of 10 pounds (4.5 kg.) of body weight was followed by wheezing and dyspnea on exertion. Physical examination revealed general glandular enlargement. From the right pleural cavity, 1,500 c.c. of straw-colored fluid, with a specific gravity of 1.020, and clotting quickly, was removed. The enlarged, definitely outlined shadow suggests a lymphomatous growth.

NECROPSY FINDINGS

Of our series of seven cases of malignant lymphoma with intrathoracic involvement which came to necropsy, six showed mediastinal involvement; three hilus nodules, two lung infiltration and one isolated nodules of lymphomatous tissue in the lungs.

I believe that the best method of approach to a problem of this kind is an interpretation of the radiographic appearances from the pathology of the disease under consideration. In any given case the pathology varies with the course of the disease, and there is reason to think that the radiographic appearances would vary also. A case which at first would come under the mediastinal or hilus type might later become infiltrating.

DIFFERENTIAL DIAGNOSIS

Lymphosarcoma.—The knowledge of the pathology of this tumor is so indefinite that lymphosarcoma cannot be said to be essentially different from Hodgkin's disease. MacCallum [11] believes that the two conditions are distinct, while Bunting [12] holds the opposite opinion. Mueller [13] has presented evidence that lymphosarcoma is a rapidly progressive form of Hodgkin's disease. The term malignant lymphoma, which many pathologists apply to Hodgkin's disease, would seem to include lymphosarcoma. We agree with Kahn [4] that the two conditions cannot be differentiated radiographically. Figures 6, 7 and 9 might very well represent lymphosarcoma.

Metastatic Sarcoma.—Metastases in sarcoma are usually blood borne. They commonly spring up in the lung parenchyma giving definite radiographic shadows in the lung fields. Figure 16 shows dense, well defined shadows at the bases, partly obscuring the heart shadow. They resemble somewhat those of Hodgkin's disease. In the latter condition, however, tumors spring up in preexisting lymph nodes, which places the shadows usually in the hilus or upper mediastinal regions.

Carcinoma.—The growths in carcinoma are in general denser and even more discrete than those of lymphoma, with the result that the radiographic shadows are more definite and have sharper outlines (Figs. 5 and 17). Metastatic carcinoma often shows isolated nodules in the lung substance which cast pronounced radiographic shadows.

11. MacCallum, W. G.: On the Pathological Anatomy of Lymphosarcoma and Its Status with Relation to Hodgkin's Disease, Bull. Johns Hopkins Hosp. **18**:337, 1907.

12. Bunting, C. H.: Lymphosarcoma, Nelson's Loose Leaf System of Medicine **3**:366.

13. Mueller, T.: Relation of Hodgkin's Disease to Sarcoma, J. Med. Res. **42**:325, 1921.

Wessler and Greene have seen radiographic evidence of isolated nodules in the lungs in four of their twenty-five cases of Hodgkin's disease. None of our cases gave this evidence on the plates, although one of the seven cases on which necropsy was performed had lymphomatous nodules in the lungs (Plate 8). MacCullum [14] found numerous large discrete nodules scattered in the lung tissue in one case at necropsy.

We believe that isolated shadows, in the lung fields, circular or oval in shape and rather dense, are good evidence against Hodgkin's disease and in favor of metastatic carcinoma or sarcoma.

Enlarged Hiluses and Chronic Inflammatory Processes.—The size of the shadows at the roots of the lungs varies so greatly that it is difficult to determine their normal limits. Every inflammation or irritation, acute or chronic, supposedly contributes to a thickening of the nodes about the lung roots.

Occasionally a hilus shadow has a distinct outline or a suggestion of lobulation which resembles Hodgkin's disease.

In Figure 18, both hilus shadows are thickened. That on the right has a distinct outline. The fact that it is not lobulated and tapers to a point toward the base of the lung is evidence against Hodgkin's disease. The patient had tertiary syphilis with dyspnea and aphonia.

Tuberculosis.—By far the most important condition to differentiate from Hodgkin's disease is tuberculosis. Tuberculosis might be considered a glandular disease, since the lymph nodes are almost constantly involved secondarily to focal infection. Many believe Hodgkin's disease has a similar origin.[12] These diseases are almost similar, both from a clinical and a pathologic point of view. This results in many erroneous diagnoses and much disadvantage to patients.

The prime reason for early differentiation of Hodgkin's disease from pulmonary or glandular tuberculosis is that roentgen-ray treatment, even though it does not cure, prolongs the lives and greatly enhances the comfort of patients with Hodgkin's disease.[13]

Comparative Pathology of Tuberculosis and Hodgkin's Disease.—There may be generalized or localized glandular enlargement in both diseases. The glands about the roots of the lungs are commonly affected in both; often in tuberculosis, and occasionally in Hodgkin's disease, they are the only glands affected,[6] so that radiographic differentiation becomes important.

The difference in the intrathoracic pathology of the two conditions is that Hodgkin's disease, so far as our investigation has been able to

14. MacCallum: Footnote 7.

Fig. 11.—Same case as in Figure 10, three months later.

Fig. 12.—Hodgkin's disease, with upper mediastinal involvement. A man, aged 28, one year ago noticed a swelling in the neck, but he had no other symptoms. Physical examination revealed shotty, discrete, bean-sized lymph nodes in the neck and axillae, with supracardiac dulness 11 cm. in the first interspace, and D'Espine's sign to the tenth dorsal vertebra. The temperature, from 99 to 100 F. for the first six days in the hospital, was reduced by roentgen-ray treatment. According to the blood count, there were from 14,000 to 19,000 white blood corpuscles, 76 per cent. polymorphonuclears, 10 per cent. lymphocytes, 14 per cent. large mononuclears. The biopsy report was: malignant lymphoma.

Fig. 13.—Same case as in Figure 12 after eight months' roentgen-ray treatment.

Fig. 14.—Hodgkin's disease; lobulated shadows at the hilums. A man, aged 32, had night sweats one year before. He lost weight and strength and coughed, but there was little sputum. He had slight dyspnea on exertion. There was no history of exposure to tuberculosis, but he was sent to Arizona. The dyspnea gradually became worse. Physical examination revealed no enlarged nodes in the neck, axillae or groins, and the chest was clear. The temperature, from 100 to 101 F. for one week, was reduced by roentgen-ray treatment. The white blood count was 18,000; there were from 73 to 82 per cent. polymorphonuclears, 5 per cent. lymphocytes and from 12 to 18 per cent. large mononuclears. The hemoglobin was 80 per cent. Figure 14 shows definitely lobulated shadows at both hilums.

Fig. 15.—Same case as in Figure 14. The roentgenogram shows the reduction in density after five months' roentgen-ray treatment.

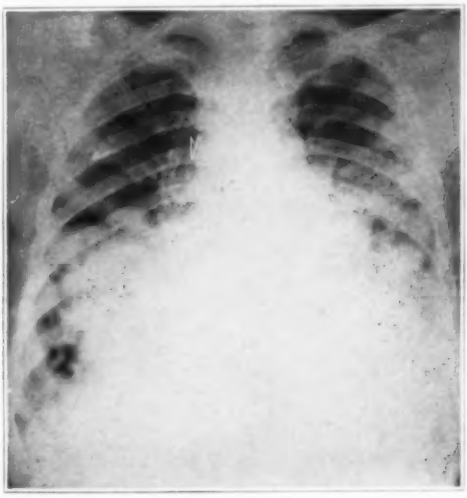

Fig. 16.—Periosteal sarcoma; metastases to lungs, with dense lobulated shadows at both bases. A boy, aged 18, had a periosteal sarcoma of the left ulna. There was dyspnea, and dulness at the bases of both lungs. From the left side of the chest, 50 c.c. of bloody fluid was taken. The biopsy report was: osteogenetic sarcoma. In Hodgkin's disease the shadows are seen higher up, in the regions of the lymph nodes—in the upper mediastinum and the hilums.

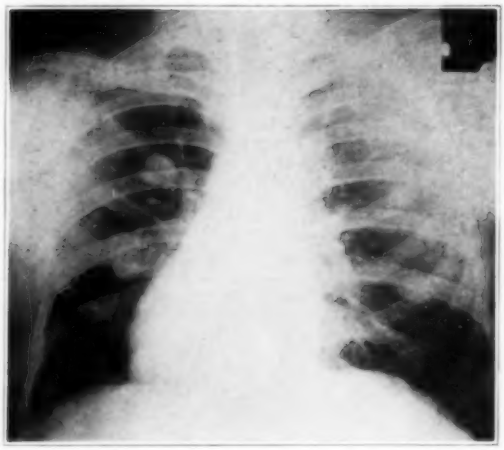

Fig. 17.—Metastatic carcinoma; dense, homogeneous, sharply outlined, circular and oval shadows in the lung fields. This illustration should be compared with Figure 8, which showed lymphomatous nodules in the lung at necropsy.

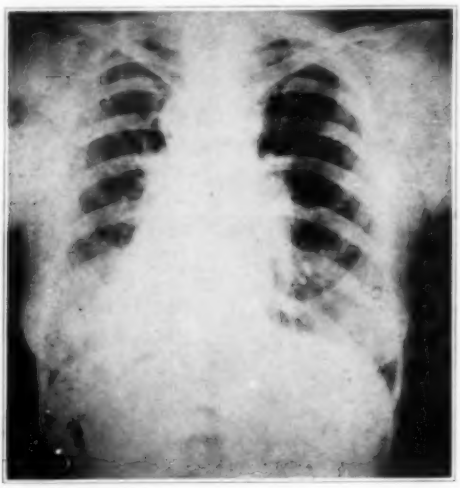

Fig. 18.—Enlarged hilum shadow due to old inflammatory processes. A woman, aged 42, had dyspnea, slightly enlarged lymph nodes in the right side of the neck, paralysis of the left vocal cord and a strongly positive Wassermann test. The biopsy report on a cervical lymph node was: tuberculosis or syphilis. A diagnosis of tertiary syphilis was made. The shadow is not definitely lobulated as in Hodgkin's disease.

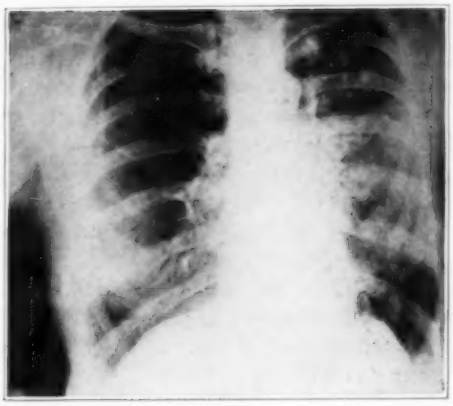

Fig. 19.—Old tuberculosis. The shadows represent calcified areas in the region of the right hilum. The pronounced mottling in the field of the left lung should be compared with Figures 6, 7 and 8.

Fig. 20.—Tuberculosis with hilum shadows resembling Hodgkin's disease. The case was clinically tuberculosis, the diagnosis not being confirmed by sputum, but owing to the suggestion of lobulation at the hilums in the roentgenogram and the lack of dense areas suggesting calcification, Hodgkin's disease was suspected. The pronounced mottling extending into the field of the right lung, however, together with the fact that the patient was up and about, made a diagnosis of Hodgkin's disease doubtful. Roentgen-ray treatment had no effect on the shadows.

show, starts in the glands of the mediastinum or hilus, which grow by expansion and produce lobulations or infiltrations, while tuberculosis in adults at least usually starts in a focus at the periphery of the lung and infects the lymphatics running to the hilus, where massive infection takes place.

Typically, the radiographic shadows in Hodgkin's disease are confined to the midportion of the chest, while in tuberculosis the mottling often extends all the way to the periphery. In acute and severe cases of Hodgkin's disease, there may rarely be some mottling of the fields of the lung. Owing to fibrosis and calcification, however, the fields of the lung in tuberculosis will show a more pronounced mottling and greater irregularity in density of shadow than in Hodgkin's disease.

In the less common hilus tuberculosis, the process may be confined to this region, but since infiltration tends to occur along the lymphatics, the radiographic shadows tend to streak out radially from the hilus, giving an irregular outline. The shadow varies markedly in density, owing to calcified nodes, caseation and irregular fibrosis.

This picture offers considerable contrast to the rather homogeneous, lobulated shadows with more regular borders seen in Hodgkin's disease.

THE ROENTGEN-RAY THERAPEUTIC TEST

One of the most useful methods of differentiating Hodgkin's disease from other conditions, especially carcinoma or tuberculosis, is the roentgen-ray therapeutic test. Blankenhorn[15] considers this to be almost diagnostic. A rapid and marked reduction in the size of the lymphoma is demonstrable by radiograph after one or two treatments, especially if the case is an early one before much fibrosis has taken place in the affected nodes. (Figs. 3, 4, 6, 7, 12, 13, 14 and 15 show the effect of roentgen-ray treatment.)

CONCLUSIONS

The roentgen ray is a feasible measure to employ as an aid to the diagnosis of Hodgkin's disease because the intrathoracic nodes are often involved in this disease, and the radiographic appearances are fairly characteristic.

In rare cases in which the lymphoma is confined to the thorax and biopsy is not possible, the roentgen ray may greatly aid the diagnosis.

Hodgkin's disease is indicated when the radiograph shows homogeneous, roughly lobulated shadows in the mediastinal or hilus regions, which shrink rapidly under roentgen-ray treatment. Tuberculosis is the most important condition to differentiate from Hodgkin's disease.

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15. Blankenhorn, M. A.: Affections of the Mediastinum, Nelson's Loose Leaf System of Medicine **3**:578.

Owing to definite differences in pathology and the resulting radiographic appearances, this can be accomplished in the majority of instances.

The most fruitful method of approach to a study of this kind is by an interpretation of the radiographic appearances according to the pathology of the diseases under consideration.

CLINICAL AND ROENTGENOLOGIC STUDY OF ONE HUNDRED AND FIVE CASES OF SYPHILIS WITH REFERENCE TO THE CARDIOVASCULAR SYSTEM *

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AND
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This paper concerns itself with the clinical and roentgenologic study of 105 patients known to be syphilitic, with particular reference to the presence of cardiovascular disease. The association of central nervous involvement with aortic disease and the specific treatment of aortic syphilis were considered to be not without interest. The roentgenologic evidence of aortic syphilis in particular is treated in an additional section by Dr. Pfahler.

The study of cardiovascular disease in syphilis received its impetus particularly by the recognition of a characteristic and frequent aortic involvement. Although the earliest systematic description of aortic syphilis is ascribed to Doehle,[1] and Heller,[2] their efforts were anticipated by Francis H. Welch [3] who, in November, 1875, read a paper on 117 cases of aortitis, in 46 per cent. of which there was a clear record of syphilis. He also reported a series of fifty-six cases of fatal syphilis, of which thirty-four presented aortic lesions. Another early contribution is that of Heiberg,[4] who, in Christiana, in 1876, reported on the relation of aneurysm and arterial disease to syphilis. Kreftings [5] has called attention to this record. Since this time an ever increasing literature has testified to the growing interest and understanding of this subject. In recent times, the earlier recognition of aortitis has been facilitated by accurate complement-fixation tests for syphilis and by roentgenologic methods. These methods of precision and the testimony of former and recent pathologic studies have revealed a high incidence

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* Roentgenologic study aided by a grant from the Research Institute of Cutaneous Medicine.

1. Doehle. Inaug. Diss., Kiel, 1885; Deutsch. Arch. f. klin. Med. **55**:190, 1895.
2. Heller, A.: Verhandl. d. deutsch. path. Gesellsch., vol. 2, 1899.
3. Welch, F. H.: Med.-Chir. Trans., Ser. 2, vol. 41, 1876.
4. Heiberg, H.: Norsk Mag. f. Laegevidensk. **6**:55, 1876.
5. Kreftings, R.: Berl. klin. Wchnschr. **47**:713, 1910.

of aortic and myocardial invasion in syphilis. A brief selection from the literature indicates the varying frequency with which this condition has been noted.

Gruber,[6] in 6,000 necropsy records, found aortic syphilis in 4 per cent. Marchand,[7] in 256 necropsies on subjects with acquired syphilis, found aortic disease in 211 or about 82 per cent. Oberndorfer,[8] in 1,436 necropsies on adults, found syphilitic aortic disease in ninety-nine cases; in forty the disease was not noted until necropsy. Stadler[9] found aortic involvement in 82 per cent. of 156 cases of syphilis in which necropsy had been performed.

Lemann and Mattes[10] studied the heart and aorta of 100 consecutive necropsies. In this series there were three aneurysms. Fifty-five of the 100 showed the aortic changes which have been described as pathognomonic of syphilis; spirochetes were found in the aorta of two cases. Warthin[11] found active lesions in the heart thirty-six times and in the aorta thirty-two times in forty-one cases at necropsy; in twenty-five of these, syphilis had not been diagnosed clinically. Lamb's[12] statistics comprise 1,024 necropsies in which forty-seven cases of aortitis were noted; ten of these were aneurysms. Syphilitic aortitis represented 14.56 per cent. of the cardiac cases which included heart conditions secondary to nephritis and hypertension. Hubert[13] stated that aortitis comprised 70 per cent. of all cases of visceral syphilis and 14.6 per cent. of syphilis in general.

The Wassermann test has been found to yield a large proportion of positive reactions in cases diagnosed as aortitis. Citron[14] elicited a positive Wassermann reaction in 60 per cent. of cases of aortic insufficiency. Of seventy-one marked cases of aortic syphilis, Oberndorfer[8] reported a positive Wassermann reaction in sixty-seven. Pearce[15] collected seventy cases of aortitis from the literature, in 78.5 per cent. of which the Wassermann reaction was positive. Eich[16] elicited a positive reaction in 81.8 per cent. of forty-four cases which showed characteristic syphilitic aortic disease at necropsy, but in some instances postmortem blood was used in the test, which renders the results doubtful.

6. Gruber, G. B.: Ueber die Doehle-Heller'sche Aortitis, Jena, 1914.
7. Marchand: Verhandl. d. deutsch. path. Gesellsch. **6**:137, 1903.
8. Oberndorfer: München. med. Wchnschr. **60**:505 (March) 1913.
9. Stadler: Syphilitic Aortenerkrankung, G. Fischer, Jena, 1912.
10. Lemann, I. I., and Mattes, A.: South. M. J. Sept., 1920, p. 623.
11. Warthin, S.: Am. J. M. Sc. **152**:508 (Oct.) 1916.
12. Lamb, A. R.: Nelson's Living Medicine, New York, T. Nelson, **4**, 1920.
13. Hubert, G.: Deutsch. Arch. f. klin. Med. **128**:317 (Feb.) 1919.
14. Citron, J.: Berl. klin. Wchnschr. **45**:2142 (Nov.) 1908.
15. Pearce, R. M.: The Wassermann Reaction in the Pathology, Diagnosis and Treatment of Syphilis, Arch. Int. Med. **6**:478 (Nov.) 1910.
16. Eich, P.: Frankfurter Ztschr. f. Path. **7**:373, 1911.

In a study of thirty-six cases of aortic disease, Cummer and Dexter [17] found a positive Wassermann reaction in twenty-seven, or 75 per cent. Of forty-seven cases examined by Longcope,[18] thirty-five or 74.4 per cent. gave a positive reaction. Schotmüller [19] in 189 patients with positive Wassermann reactions, found aortitis twenty-eight times. Hubert [13] studied 220 patients with syphilitic aortitis; in 85 per cent. of 186 cases, the Wassermann reaction was positive. Brown [20] noted seven cases of aortitis in 136 patients giving a positive Wassermann reaction.

The presence of the spirochete in the diseased aorta furnished a striking demonstration of its etiologic significance. Reuter,[21] in 1906, described the finding of the spirochete in the wall of the affected aorta. Benda,[22] Schmorl [23] and Wright and Richardson [24] also demonstrated the spirochete in the heart and aorta of syphilitic persons. Larkin and Levy [25] considered the demonstration of spirochetes in these lesions as doubtful, and Longcope stated they could not be demonstrated constantly. Warthin,[26] in 1911, found the heart wall crowded with spirochetes in congenital syphilis in nine infants and young children who came to necropsy. In later publications he emphasized the persistence of the organism in the heart and aorta of patients free from symptoms.

The clinical features of the disease were reviewed by Longcope [14] in 1913 in a comprehensive article based on the study of sixty-three patients, of which twenty were treated with arsphenamin. The systematic description of aortic dilatation was given by McCrae,[27] who noted a definite proportion of these cases to be due to syphilis.

PATHOLOGY OF AORTITIS

Grossly, there are a number of characteristics which distinguish the syphilitic aorta from the plaques of simple atheroma. The changes in syphilitic aortitis usually appear near and above the valves (supra-sigmoid aorta) and tend to spread upward along the transverse arch and down to the aortic leaflets. There is a wrinkled appearance of

17. Cummer, C. L., and Dexter, R. D.: The Relation of Aortitis to Syphilis and the Importance of Its Recognition, J. A. M. A. **59**:419 (Aug. 10) 1912.
18. Longcope, W. T.: Syphilitic Aortitis: Its Diagnosis and Treatment, Arch. Int. Med. **11**:15 (Jan.) 1913.
19. Schotmüller, quoted by A. R. Lamb: Nelson's Living Medicine, **4**:533.
20. Brown, G. E.: Am. J. M. Sc. **157**:41 (Jan.) 1919.
21. Reuter: München. med. Wchnschr. **53**:778, 1906.
22. Benda: Berl. klin. Wchnschr. **43**:989, 1906.
23. Schmorl: München. med. Wchnschr. **54**:188, 1907.
24. Wright, J. H., and Richardson, O.: Boston M. & S. J. **160**:539, 1909.
25. Larkin, J. H., and Levy, I. J.: J. Exper. M. **23**:25 (Jan.) 1916.
26. Warthin, A. S.: Am. J. M. Sc. **141**:398 (March) 1911.
27. McCrae, T.: Am. J. M. Sc. **140**:469 (Oct.) 1910.

the intima and there are numbers of isolated or confluent grayish translucent or yellowish nodular areas, some of which have cicatricial puckering in the center. Unless there is a secondary deposit of calcareous material, the lesions do not resemble the areas of calcified plaques nor ulcerations usually seen in the more distal portions of the aorta in atheroma. The walls of the affected portion of the aorta are thinned out in places, with small aneurysmal pouchings. There is often thickening and shrinking of the aortic valves and narrowing around the mouths of the coronary vessels. The ascending aorta may be uniformly dilated, with involvement of the aortic valves. This type of diffuse aortic dilatation was described as early as 1815 by Hodgson [28] and is systematically described in its relation to syphilis by McCrae.[27]

Microscopically, the lesions are seen to be inflammatory and not of a degenerative character as in atheroma. There are areas of infiltration about the vasa vasorum in the adventitia and media with lymphoid cells, plasma cells and giant cells; there is fragmentation of the elastic tissue with replacement by fibrous tissue containing wandering cells. The intima may show a thickened fibrous change, but there is little fat or calcium deposit as in atheroma. The peri-adventitial lymph nodes have been noted to be enlarged in conjunction with these lesions. The predilection of the spirochete for the proximal aorta has been explained by Klotz [29] to be due probably to the rich network of lymphatics draining the outer wall of the aorta and communicating with large lymph channels. Though it is argued by some observers that the predilection for the lymphatic drainage bed in the thorax remains to be explained, it appears to be be an important observation.

SYMPTOMATOLOGY

The symptoms of aortic syphilis are: thoracic pain—usually substernal or precordial—dyspnea, palpitation of the heart, cough, changes in voice, weakness, edema of the ankles and sometimes loss in weight. The thoracic pain may take on the characteristics of a true angina with radiation of pain down the left arm, or may be complained of as merely a sense of oppression in the chest. The dyspnea may in some cases be of a paroxysmal nature. It is of vital importance that cardiac syphilis be diagnosed at the earliest possible time. When one considers the long period between the time when the heart and aorta are invaded to the frank development of subjective and objective symptoms, it becomes apparent that comparatively minor signs are sufficient to warrant a presumptive diagnosis. These early signs may be confined to some tenderness over the manubrium, a systolic murmur at the aortic area

28. Hodgson, J.: A Treatise on the Diseases of the Arteries and Veins, London, 1815.

29. Klotz, O.: Am. J. M. Sc. **155**:92 (Jan.) 1918.

and an accentuated wooden-like aortic second sound. In the stage of dilatation, however, the signs are numerous. Pulsations are noted in the carotid arteries, in the suprasternal notch, subclavian arteries and sometimes in the second and third interspaces on either side of the sternum. The veins are prominent over the chest and at times suffusion of the tissues above the clavicle is noted. The pulsation of the right subclavian artery becomes easily palpable. There is increased supracardiac dulness, and a systolic murmur is commonly heard at the aortic area and transmitted to the carotids. The aortic second sound takes on a peculiar accentuated mellow sound likened by Allbutt [30] to the "tabourka" or Algerian drum and described by McCrae as a wooden bell-like note. If there is aortic insufficiency, a diastolic murmur is noted and is heard best along the edge of the sternum. The well known collapsing type of pulse is characteristic at this stage. The cardiac impulse is extended downward and to the left.

With a sacculated aneurysmal dilatation there are noted in varying degree the added signs of mediastinal pressure, difference in pulses, tracheal tugging, inequality of the pupils, hoarseness, aphonia or brassy cough. If the lesion is in the ascending arch, a pulsating tumor may present itself in the upper part of the chest.

INCIDENCE OF AORTIC AND MYOCARDIAL DISEASE IN 105 SYPHILITIC PATIENTS

Male patients only were studied; of these, sixty were white and forty-five were negroes. They varied in age from 22 to 59 years, and the duration of syphilitic infection varied from one to twenty or more years. Approximately, one-fourth were between 40 and 50 years of age. In establishing a clinical diagnosis of aortitis, a sufficient number of the signs and symptoms described above were elicited before the patient was considered to present well-defined aortic disease. The association of corroborative evidence by roentgenoscopy was noted. Of the 105 patients, twelve were found to be suffering from aortic or myocardial disease. Of these, three were white and nine were negroes. Of the aortic lesions, one was diagnosed as aortitis, two as aortic dilatation, six as aortic dilatation and insufficiency and two as aneurysm. A brief outline of the histories of some of these patients is given under the heading of treatment. The ages of 11 of these patients ranged from 37 to 57 years; the comparatively early appearance of aortic insufficiency in the twelfth patient at the age of 30 is explained by the fact that infection occurred at the age of 15. The Wassermann reaction was four plus in all these patients except one with aortic dilatation, in whom the reaction was plus three.

30. Allbutt, Sir T. C.: Disease of the Arteries, London, Macmillan Co., 1915.

We have not assumed that the number of aortic cases represents the true proportion of definite lesions among a group of syphilitic persons due to the fact that a number of these patients were recognized to have aortic disease in medical clinics and were therefore included when the Wassermann reaction was reported to be positive.

"WASSERMANN-FAST" SYPHILIS AND CARDIAC SYPHILIS

The statement has frequently appeared in the literature that syphilitic patients with persistently positive Wassermann reactions are particularly likely to have cardiac syphilis or neurosyphilis. This has not been in strict accord with our experience. The term "Wassermann-fast," it appears, has been used without discrimination; it has no definite significance, but only a relative one, since it implies a Wassermann reaction which remains positive in spite of treatment—to what amount of treatment would be variably stated by different observers. We have heard it used in reference to a positive reaction after as few as fifteen injections of arsphenamin; others apply the term to those cases in which the reaction is positive in spite of a considerable number of injections—fifty or more. As a matter of fact, the greater the amount of treatment the less percentage of "Wassermann-fast" reactions will be observed. It is, therefore, desirable to qualify the term "Wassermann-fast" by stating to what amount of treatment the reaction is persistently positive.

We have observed many syphilitic patients whose Wassermann reaction was persistently positive in spite of considerable antisyphilitic therapy, in whom no cardiac involvement or neurosyphilis could be clinically demonstrated. Perhaps the best example of this group is represented in the subject of congenital syphilis in whom the Wassermann test notably remains positive in spite of treatment. It is not our purpose to discuss the "Wassermann-fast" case so far as neurosyphilis is concerned; but it may be stated that, excluding paresis, it is not uncommon to observe a negative blood Wassermann reaction in patients with neurosyphilis.

ARTERIAL FIBROSIS

The picture of syphilitic disease of the peripheral arteries represents the same process as that in the large vessels. It has been noted universally that arterial thickening, especially when occurring prematurely, is a prominent feature of this infection. Indeed, this factor in the causation of arteriosclerosis was being overemphasized until the studies of Thayer,[31] Klotz,[32] and others demonstrated that many infections

31. Thayer, W. S.: Am. J. M. Sc. **127**:391 (March) 1904.
32. Klotz, O.: Arteriosclerosis, Lancaster, New Era Pub. Co., 1911.

(notably typhoid fever) are prone to inflict injuries on the artery, resulting in noticeable thickening. In ascribing any radial thickening in a series similar to the one under discussion, it is obviously advisable to rule out if possible the factors of hypertension, infections other than syphilis, chemical poisons and the degenerative atherosclerosis termed "decrescent arteriosclerosis" by Allbutt. With these exceptions in mind, there were noted sixteen patients of the total number of 105 who presented changes varying from arterial thickening to marked sclerosis. Twelve were in an age period in which decreascent atherosclerosis would be unlikely. It is a familiar observation that changes may occur in peripheral or cerebral arteries without clinically demonstrable lesions in the aorta. Conversely, aortic lesions are noted without concomitant changes in the radials. However, in this series, seven of the eleven patients with known aortic cases presented radials varying from definite thickening to actual sclerosis.

BLOOD PRESSURE

Syphilis apparently plays no part in the common type of vascular hypertension (hyperpiesia), especially of the climacteric group. In the present series of 105 patients hypertension ranging from 180 to 200 mm. of mercury, systolic pressure, was noted only seven times. It appears that a slight rise in pressure was present in some of the patients showing aortic lesions with, however, a marked amplitude of pulse pressure in the patients with aortic insufficiency. Whether the added vascular tension predisposed to aortic changes or was a manifestation of the lesion seemed to be a question for each individual case.

A definite state of lowered pressure, especially when the age period is considered, existed in thirty cases, or nearly one third of the total number. Fifteen of these thirty patients had systolic pressure at 100 mm. of mercury or below. Demetre [33] has recorded a state of lowered arterial tension in tabes, although the figures given in this table fall into a range which we have considered might be noted in normal cases. In one third of thirty patients with neurosyphilis in the present series, the arterial tension was below a systolic pressure of 120. It is possible that vascular hypotension is an index of the asthenia noted in some of the patients suffering from tabes.

ASSOCIATION OF THE AORTIC DISEASE AND NEUROSYPHILIS

The association of aortic involvement with neurosyphilis has been noted by various observers, although they have not been in accord as to the frequency of this coincidence. Berger and Rosenbach,[34] in

33. Demetre, M. P.: Bull. et mém. Soc. méd. de hôp. de Paris **9**:349 (March 17) 1921.

34. Berger and Rosenbach: Berl. klin. Wchnschr. **27**:402, 1879.

1879, described the association of tabes and aortic insufficiency. Fournier,[35] Grasset [36] and Letulle [37] were of the impression that aortic disease was rare in tabes. Charcot [38] and Vulpian,[39] particularly, considered the association relatively frequent. Ruge and Hüttner [40] found nine cases of aortic insufficiency among 138 tabetic paients. Nordman [41] reported eight cases of aortitis among 100 tabetic persons. Hertz,[42] in ninety-eight cases of tabes, noted six cases of aortic insufficiency, two of aneurysm and sixteen cases of aortic dilatation, while in another series he found forty-eight cases of aortic insufficiency among seventy-six tabetic persons. Hubert [13] found tabes in 25 per cent. of 220 cases of aortitis. Guilly [43] in 200 patients with paresis found evidences of aortic disease at necropsy in forty-one. A recent and comprehensive report of this question by Friedman [44] gives the results of a similar study in three series. In one series of fifty cases of tabes, he noted seven patients with cardiovascular disease. In the second series of forty cases of neurosyphilis, there were seven instances of cardiovascular involvement. In the third series derived from postmortem records of the State Hospital for the Insane at Morristown, N. J., 1907 to 1915, he selected eighty-three cases of paresis in patients about 45 years of age or less; in this group he found forty-nine with changes in the aorta indicative of syphilis and also similar changes in thirteen of the older patients, making a total of sixty-three cases in which there was aortic disease, or 75 per cent.

Although the small number of patients with neurosyphilis in our own series precludes the attachment of much significance to a similar analysis, we can record one marked case of aortic insufficiency among five patients with paresis and three cases of widening of the ascending arch of the aorta in another group of twenty patients with neurosyphilis, of whom eleven were tabetic patients. From these figures we cannot infer any unusual frequency or rarity of the coexistence of these two types of syphilitic involvement. It may be of significance to note, however, that in the patients presenting marked and severe cardio-

35. Fournier: Traite de la Syphilis, 1899.
36. Grasset, quoted by Bouveret, Lyon méd. **43**:235, 1885.
37. Letulle: Gaz. méd. de Paris **39-40**:504, 1880; Presse méd. **4**:605, 1896.
38. Charcot, quoted by Friedman: On the Associated Incidence of Syphilis of the Central Nervous System and Cardiovascular Syphilis, Arch. Neurol. & Psychiat. **1**:289 (March) 1919.
39. Vulpian: Mal. du Syst. Nerveux 377, 1889.
40. Ruge and Hüttner: Berl. klin. Wchnschr. **34**:760, 1897.
41. Nordman: Le coeur de tabetique, Théses de Paris, 1895.
42. Hertz: Les nerfs du coeur chez les tabetiques, Théses de Paris, 1903.
43. Guilly: Théses de Paris, No. 57, 1904-1905.
44. Friedman, E. D.: On the Associated Incidence of Syphilis of the Central Nervous System and Cardiovascular Syphilis, Arch. Neurol. Psychiat. **1**:289 (March) 1919.

vascular involvement, neurosyphilis was noted only once, whereas the total number of patients with neurosyphilis comprised nearly one fourth of the total series.

There is a well-known dogma to the effect that syphilitic patients rarely present clinical manifestations of tertiary syphilis involving different systems. This statement holds true in the majority of patients with tertiary syphilis whom we have examined. It is not uncommon, however, to observe syphilitic patients with active tertiary manifestations, who also present one or more neurologic abnormalities, a normal spinal fluid and the absence of subjective symptoms of neurosyphilis. These findings in all likelihood represent a scar of a former neurologic process. It appears that syphilis in the majority of cases is expended in only one system of the body. The work of Warthin, however, has shown that pathologically this is the exception rather than the rule. It can appropriately be recalled here that those who advocate the existence of separate strains of spirochaetes point to the aforementioned dictum in support of their theory.

TREATMENT

The favorable effect of specific treatment on aortic syphilis in all its stages has been noted in most of the writings on this subject. Without reviewing the considerable literature on this phase of the subject, the recent reports of Elliott [45] in particular, are of interest. Also MacLachlan [46] has recently reported good results in a small series of patients with aneurysm by the use of arsphenamin combined with rest, diet and other medical measures. In order to avoid untoward effects we start treatment with mercury in the form of inunctions or the yellow mercurous iodid by mouth, for a period of six weeks. The possibility of a Herxheimer reaction,[47] which may occur after an initial injection of arsphenamin, is also rendered less likely by this procedure. We can appropriately mention the following observation:

Some years ago a patient with an aneurysm previously untreated was given a full dose of arsphenamin. Within the following twenty-four hours death suddenly ensued; necropsy revealed a ruptured aneurysm. This occurrence has been properly called a local Herxheimer reaction.[48]

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45. Elliott, A. R.: Am. J. M. Sc. **154**:14 (July) 1917; Med. Clin. of North America **1**:1305 (March) 1918.

46. MacLachlan, W. W. G.: Am. J. M. Sc. **159**:525 (April) 1920.

47. Herxheimer and Krause: Deutsch. med. Wchnschr. **27**:895, 1902.

48. In the treatment of secondary syphilis with arsphenamin, the phenomenon of the Jarisch-Herxheimer reaction is observed. This reaction, as originally described, was a local one—an accentuation, reddening and swelling of the macular and papular rashes occurring within twenty-four hours after the use of mercury. Besides this "local" reaction, Neisser mentions a general one after treatment with arsphenamin which is characterized by transitory increase of the headache in cerebral syphilis and of the lighting pains in tabes.

(Footnote 48 continued on next page)

If the patient was doing well, he was admitted for observation during the period of arsphenamin treatment. Minimal doses of 0.1 or 0.2 gm. neo-arsphenamin increased up to 0.3 or 0.4 gm. (and up to 0.6 gm. in the favorable cases) were given once or twice a week. After about six to ten injections, improvement was sufficiently noticeable and the person continued the treatment as an ambulatory patient. Digitalis was given when indicated. At times striking changes in the subjective symptoms were noted. Dyspnea, pain and cough were usually relieved, and the disability of the patient was lessened. The duration of the arsphenamin treatment was not constant in all cases, frequently owing to the fact that the patients after amelioration of symptoms were apt to stay away from the clinic.

However, the aim has been to continue the use of mercurials in between series of arsphenamin injections. The use of intramuscular injections of mercuric succinimid or salicylate at weekly intervals is of value. As a rule, physical signs remain practically unchanged even in the face of subjective improvement, although at times pulsations in the neck and to the sides of the sternum may grow less. The characteristic results in some of the patients suffering from well advanced aortic disease are noted in brief outlines.

ROENTGENOLOGIC STUDIES

Roentgenologic Evidence of Syphilitic Aortitis.—Assman[49] gives these causes of enlargement of the aorta: (1) old age—physiologic; (2) atheromatosis; (3) syphilitic aortitis, and (4) cardiac disease: (*a*) in nephritis—due to high blood pressure, (*b*) aortic insufficiency and (*c*) isthmus stenosis of the aorta.

He says that in middle age with no cardiac lesion and no high blood pressure one should consider syphilitic aortitis. In twenty-seven cases proved by necropsy, the width of the aortic shadow was approximately 5.5 cm. as compared with the normal, about 3.5 cm.

The two leading signs of syphilitic aortitis are dilatation in the first portion and abnormal pulsation. The dilatation may be local or diffuse; with diffuse dilatation the density is increased. If calcification has taken place, dense plaques may be seen.

Increased pulsation is due to high blood pressure, aortic insufficiency and stenosis at the isthmus and to thinning of the walls in syphilitic

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At the present time the term "Herxheimer" reaction is used in a still more general way than Neisser's "general" reaction. It is given as the explanation of the provocative Wassermann reaction. It is used to explain local reactions other than in the original sense, for instance, a rupture of an aneurysm following the administration of arsphenamin, etc. Mercury is a less powerful spirocheticide than is arsphenamin and is, therefore, less likely to produce a Herxheimer reaction.

49. Assman: Die Klinische Roentgendiagnostik der Inneren Erkrankungen, Leipzig, Vogel, p. 115.

aortitis. Even in syphilitic aortitis with diffuse dilatation there is apt to be some localized dilatation also, especially immediately above the aortic valves.

Elliott [45] says: "Of all the methods of diagnosis to determine the presence of aortic disease, the roentgen ray is the most valuable."

In aortitis, the roentgen ray reveals two kinds of changes: alterations in density of shadow and changes in contour. In early aortitis,

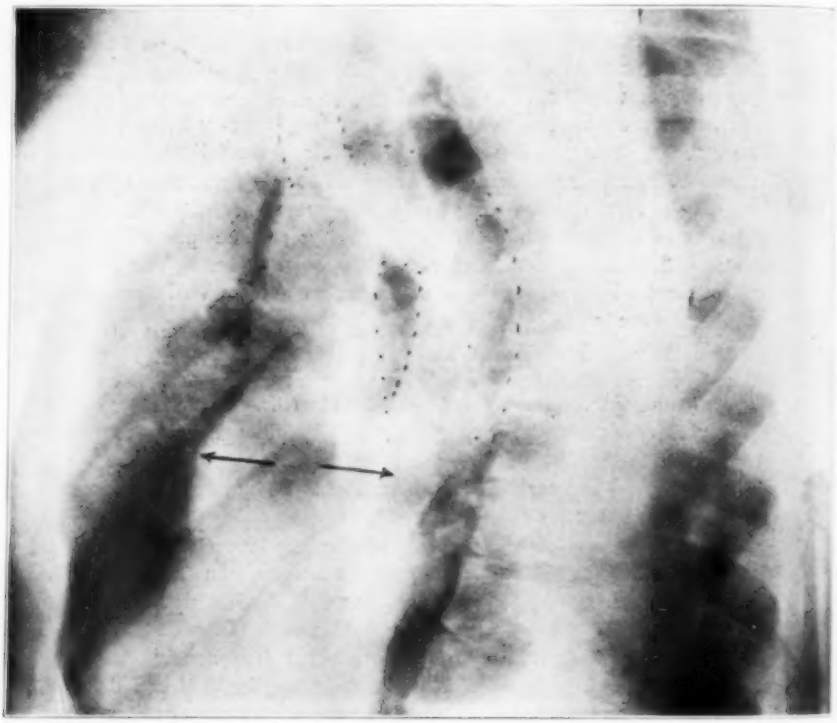

Fig. 1.—An oblique view showing well marked dilatation of the first portion of the arch.

the pathologic process is confined to the origin of the aorta. As the vessel at this stage is not thickened and no lime salts exist, there may be merely a slight dilatation of the first part of the arch, with exaggerated pulsation at that point.

Some dilatation of the aorta is quite common in aortic sclerosis, but this is likely to affect the entire aorta, and the entire aortic shadow is increased.

In aortic dilatation due to high blood pressure, there is likely to be associated hypertrophy of the left ventricle. In early aortitis there is no enlargement of the heart unless there is an associated valve defect or hypertension. In aortitis, the aortic shadow is likely to increase to the right above the shadow of the right auricle.

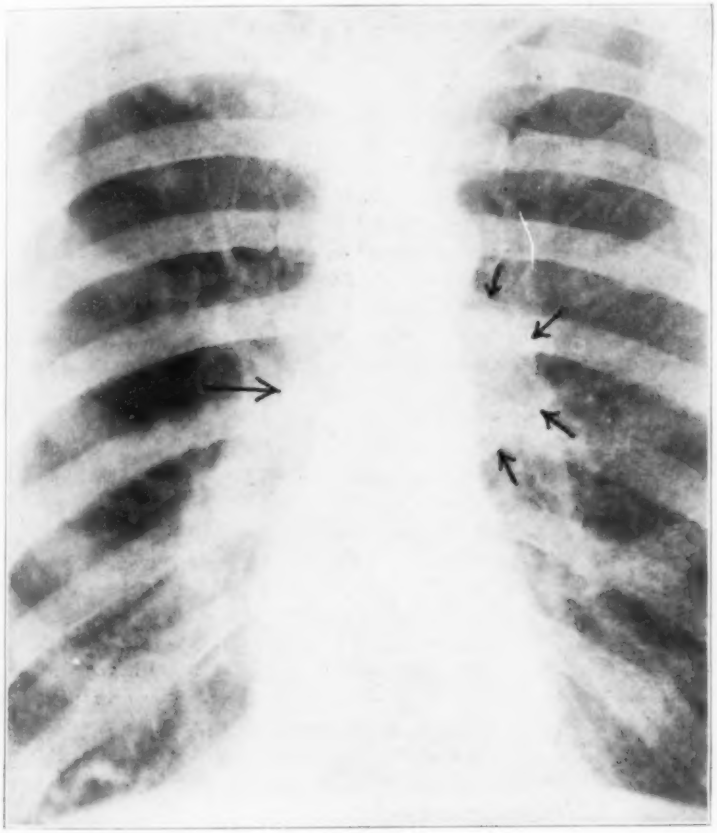

Fig. 2.—Moderate dilatation of the first portion of the arch on the right and an abnormal mass at the root of the left lung, probably a gumma.

If the disease involves the entire arch, one must expect a dilatation of the entire arch, with a total increase in the width; but one is not likely to have the buckling or knob observed as the result of the elongation which occurs in arteriosclerosis. If the disease extends to the innominate or common carotid, these vessels are likely to be dilated and give increased shadows.

Holmes and Ruggles [50] say, "A marked prominence of the aortic shadow to the right is almost always due to specific aortitis."

McGraven and Scott [51] argue that since the cardiovascular system is the most frequent and vulnerable point of attack for the spirochetes, every syphilitic patient should be suspected of having aortic or cardiac involvement. Levison says, "The earliest x-ray evidence should be looked for at a point where pathological lesions are most common, that is, just above the semilunar valves in the suprasigmoid part of the aorta."

Our observations have been based on the study by fluoroscope and teleoroentgenograms made at a distance of 2 meters, and oblique films in sixty-three patients who were known to be syphilitic. We found that the age ranged from 20 to 25 in eight cases, from 25 to 30 in nine cases, from 30 to 35 in thirteen cases, from 35 to 40 in eight cases, from 40 to 45 in four cases, from 45 to 50 in eight cases, from 50 to 55 in eleven cases and from 55 to 60 in two cases. The roentgenograms showed that the heart and aorta were normal in twenty-three cases, probable aortitis in nineteen cases, syphilitic aortitis in eighteen cases and aneurysm in three cases—of the first portion in one case, of the arch in one case and of the descending portion in one case.

The cases classed as probable syphilitic aortitis showed the roentgenologic evidence of aortitis, but had associated cardiac disease, hypertension, or were not quite characteristic. However, since the pathologic reports on similar cases give a high percentage of positive diagnoses of syphilitic aortitis, it is quite likely that this doubtful group should be counted as positive. However, excluding these, the figures would then give syphilitic aortitis in 28.5 per cent. and aneurysm in 4.7 per cent. of our cases.

These conditions were found in the lungs: pulmonary syphilis in one case, probable pulmonary syphilis in five cases, normal lungs in forty-two cases, probable tuberculosis in one case, calcified bodies in two cases. The condition in twelve cases was not reported.

It would seem from these studies that it is important to make a careful roentgenologic study in every patient with syphilis who has any chest symptoms, no matter how slight.

REPORT OF CASES

Case 1.—J. S., a negro, aged 52 years, had an initial lesion at the age of 26. The present complaints were: substernal pain, dyspnea, cardiac palpitation and cough. The supracardiac dulness was widened to percussion, and a double aortic murmur was heard, the diastolic element of which was well transmitted down the left border of the sternum. There was moderate left-sided hyper-

50. Holmes, G. W., and Ruggles, H. E.: Roentgen Interpretation, Philadelphia, Lea and Febiger, 1921.

51. McGraven and Scott: Ohio State M. J. **18**:477 (July) 1922.

trophy. The blood pressure was: systolic, 115; diastolic, 25. The blood Wassermann test was + + + +. The roentgen ray and fluoroscope showed widening of the aorta and left-sided hypertrophy. After preliminary trial with yellow mercurous iodid and moderate doses of digitalis, he received injections of neo-arsphenamin in graded dosage up to 0.6 gm.

Amelioration of the cough, dyspnea and pain was noted after three or four injections. One year after treatment, he reported no return of his symptoms.

Case 2.—J. F. a negro, aged 30 years, gave a history of a chancre at the age of 15. When first seen he was suffering with dyspnea of six months' duration, with orthopnea for the past three months. Cough and soreness over the precordium had been noted, and he had been unable to work for about five months. The examination, in brief, revealed marked pulsations of the carotids, aortic dilatation with insufficiency and increased size of the heart. The fluoroscope outlined a dilated ascending aorta and the teleoroentgenographic measurements were: right base, 7 cm.; left base, 6 cm.; aortic area, 7 cm.; the cardiothoracic ratio was 73 per cent.

The blood Wassermann was + + + +. The blood pressure was: systolic, 120; diastolic, 40, showing the characteristic amplitude of pulse pressure. After preliminary treatment with mercurous iodid, rest and digitalis, he received, while under observation in the ward, a series of six intravenous injections of neo-arsphenamin, starting with 0.2 gm. and increasing to 0.5 gm. He then continued the injections from the outpatient department for six more doses. There was marked subjective improvement which persisted up to six months, despite the fact that he was in another city most of this time.

Case 3.—P. G., a negro, aged 37 years, could give no definite statement as to duration of disease. He complained of substernal pain radiating down the left arm, dyspnea, marked palpitation and cough. Examination revealed marked pulsations in the neck, particularly of the right carotid, increase in supracardiac dulness, wooden-bell-like aortic second sound and a short aortic systolic murmur. The blood pressure was: systolic, 150; diastolic, 100. The signs indicated aortic dilatation, but nothing indicative of aortic insufficiency. Roentgenoscopy showed dilatation of the ascending arch of the aorta. Under a regimen much as outlined in the first two cases, he noted marked lessening of pain, cough and dyspnea. The improvement was known to have persisted for at least nine months.

Case 4.—B. S., a negro laborer, aged 52 years, had had an initial lesion at the age of 19. For the past two years he had complained of persistent substernal pain, dyspnea and an audible wheezing in the chest. He noticed dysphagia at times. Examination and roentgenoscopy revealed a large aneurysm of the ascending aorta. The blood Wassermann reaction was 4 plus. The treatment was similar to that in preceding cases, the highest dose of neo-arsphenamin being 0.4 gm. There was noticeable amelioration of pain and dyspnea, and against advice the patient went back to laboring work. He returned in several months with most of the original complaints, but with rest, digitalis medication and six injections of neo-arsphenamin, he improved sufficiently to undertake light work.

Case 5.—C. E., a negro, aged 42, had a doubtful history of chancre at the age of 18. He had never received treatment and complained at first observation of cough, dyspnea and pain down the left arm. There was sclerosis of the peripheral arteries, and heaving pulsations were noted in the carotid and subclavian arteries. The supracardiac dulness measured 8 cm. The teleoroentgenographic measurements were: heart length, 19.2 cm.; right base, 6.2 cm.; left base, 6.0 cm.; heart width, 18.8 cm.; aortic area, 4.7 cm. to the right and 4.2 cm. to the left. The cardiothoracic ratio was 73 per cent., indicating marked increase of cardiac outline. A systolic and diastolic murmur was noted over the aortic area; a mitral systolic murmur probably due to relative insufficiency was also noted. The blood pressure was: systolic, 185; diastolic, 85.

The blood Wassermann test was + + + +. Management similar to that in the foregoing cases produced some amelioration of symptoms. After going about his work a return of his symptoms was noted, but on continued mercurial, arsphenamin and digitalis medication, he remained fairly comfortable.

SUMMARY

A brief review of the literature on cardiovascular syphilis is made.

The pathology of syphilitic aortitis is discussed.

The symptomatology of syphilitic aortitis is presented with particular reference to early symptoms. The importance of an early diagnosis is emphasized.

Of a group of 105 male syphilitic patients studied by clinical methods, sixty were white and forty-five were negroes. They varied in age from 22 to 59 years, and the duration of syphilitic infection varied from one to twenty or more years. Approximately, one fourth were between 40 and 50 years of age. Twelve patients, approximately 10 per cent., were found to be suffering from aortic or myocardial disease. Of these, three were white and nine were negroes. Of the aortic lesions, one was diagnosed as aortitis, two as aortic dilatation, six as aortic dilatation and insufficiency and two as aneurysm.

Of sixty-three patients studied by roentgenologic methods, aortic disease (including aneurysm) was noted as being definitely present in nineteen, or 33 per cent. Roentgenologic examination included fluoroscopy, teleroentgenograms made at a distance of 2 meters and oblique films. The higher percentage of patients with aortic disease discovered by roentgenologic examination is in accord with pathologic studies reported by others and reviewed in this report.

The so-called Wassermann-fast syphilitic patient is discussed with particular reference to cardiac syphilis.

Of a total number of twenty-five patients with neurosyphilis, there was an associated aortic disease in four. The relative infrequency of an active syphilitic process involving one or more systems in the same patient is discussed.

THE INFLUENZA EPIDEMIC AT CAMP DEVENS IN 1918

A STUDY OF THE PATHOLOGY OF THE FATAL CASES *

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It may arouse wonder that another contribution to this much discussed subject should be offered so long after the subsidence of the pandemic form of this disease in view of the excellent reports on the pathology of the disease already presented by numerous investigators, including Goodpasture and Burnett,[1] Goodpasture,[2] Winternitz,[3] Klotz,[4] MacCallum,[5] and Opie and associates.[6] Excellent material, however, was obtained at Camp Devens during the epidemic, and although Wolbach [7] has published a preliminary report on the pathology and bacteriology of these cases, the more complete study of this material has only just been made. As this study has brought out some interesting points which have not been emphasized by other workers, and as it is possible from this material to form a definite opinion in regard to the course of the lesions in the different organs and their relation to various bacteria present, it seems advisable to publish the results.

We appreciate that a decided difference of opinion exists in regard to the cause of this pandemic. The discussion has practically narrowed down to the question of whether the influenza bacillus or some unknown virus was the etiologic agent. Excellent points have been made both

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1. Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**:177 (April) 1919.
2. Goodpasture, E. W.: The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza, Am. J. M. Sc. **158**:863 (Dec.) 1919.
3. Winternitz, M. C.; Wason, I. M., and McNamara, F. P.: The Pathology of Influenza, Yale Univ. Press, 1922.
4. Klotz, O.: Studies on Epidemic Influenza. Univ. Pittsburgh School of Medicine Publications, 1919.
5. MacCallum, W. G.: Pathological Anatomy of Pneumonia Associated with Influenza, Johns Hopkins Hosp. Rep. **20**:149, 1921.
6. Opie, E. L.; Freeman, A. W.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Pneumonia Following Influenza, J. A. M. A. **72**:556 (Feb. 22) 1919.
7. Wolbach, S. B.: Comments on the Pathology and Bacteriology of Fatal Influenza Cases as Observed at Camp Devens, Mass., Johns Hopkins Hosp. Bull. **30**:104 (April) 1919.

for and against the influenza bacillus as the causative agent. No attempt will be made to make a summary of these points or to refer to all the publications on the subject. Attention is called to the recent publications by McIntosh [8] with their complete list of references.

It is at the present time an unsettled point whether lung involvement is due to the virus of the epidemic disease or is dependent on some secondary invading organism. However, it is agreed by all that no matter what the etiology of the epidemic may be, it renders the lower respiratory tract susceptible to invasion by other organisms. As involvement of the upper respiratory tract and bronchi in this disease with productions of characteristic sputum is generally conceded, and as special pulmonary lesions have been pointed out by Goodpasture,[2] Wolbach [7] and others, that are not seen in other inflammatory conditions of the lungs, it seems reasonable to assert that the virus of this epidemic disease will cause pulmonary lesions in some cases without the presence of complicating organisms. That important pulmonary lesions do not occur in the majority of cases has been established by the clinical course of the disease, for during the epidemic the large majority of the cases ran the course of a self-limited acute febrile infection without signs suggestive of a lung involvement. However, in a considerable percentage of cases, about 25 per cent., the process extends from the bronchi into the lung tissue. It is unlikely that this disease results fatally without pulmonary involvement.

Although this study failed to establish the cause of the epidemic, it brought out certain points in regard to the relationship between the various bacteria present and the epidemic disease, so that a discussion of the etiology of this disease has been included. For example, in this study certain pulmonary lesions have been found which are considered characteristic of this epidemic disease. These lesions were present in all but one of the cases studied, and yet in this group there was no one bacterium always present. In the one case in which the characteristic pulmonary lesions were not found, death did not occur until over four weeks after the onset of the disease, and the early lesions in the lungs had been replaced and obscured by secondary infections and repair. The influenza bacillus was found more frequently than any other bacterium, and yet it was not recovered by culture or found in the sections [9] of the lungs in a small percentage of the cases. Furthermore in one instance in which this peculiar pulmonary reaction was found in the uncomplicated state, no bacteria could be demonstrated at the site of these characteristic pulmonary lesions. The inconstancy of the presence

8. McIntosh, J.: Studies in the Etiology of Epidemic Influenza. Special Report, Series 63. Privy Council, Medical Research Council, 1922.

9. In this study, bacteria were looked for in sections which were prepared with the Giemsa stain.

of the influenza bacillus and the absence of bacteria at the site of the uncomplicated pulmonary lesion suggest that some undiscovered virus produces these lesions in the lungs and presumably therefore is the cause of the epidemic.

The bacterium cultivated by Olitsky and Gates [10] from cases of this epidemic disease, and called *Bacillus pneumosintes*, has been recently advanced as the unknown virus which produces this disease. Its demonstration in sections of lungs of influenza has not yet been achieved.

For those who feel that the influenza bacillus causes the epidemic, these characteristic pulmonary lesions which were found without the presence of the influenza bacillus make it necessary to attribute to this organism the power to produce this injury to the lung before the bacilli themselves reach the alveoli. This might be accomplished by the mechanical action on the alveoli of a peculiar exudate in the bronchi and alveolar ducts due to the influenza bacillus or through toxins from these bacilli affecting the lungs. However, as mentioned above, in certain of these cases the influenza bacilli were neither found in the tissues nor recovered in cultures.

CASES STUDIED

In this series twenty-seven cases were studied. One of these patients died of a streptococcus septicemia two days after the onset of the illness. The clinical course in this case was quite different from that of other epidemic cases, and the lungs at necropsy were free from anything suggesting pneumonia of any type. Streptococci were found in the blood vessels throughout the body. For these reasons this case has been omitted from this discussion, as it is thought that the patient did not have the epidemic disease.

NECROPSY FINDINGS

On gross inspection, certain lesions were found in various parts of the body in this group of cases, some of which, especially those in the lungs, were quite characteristic of this epidemic disease. As our endeavor has been to discover the sequence of events in the lesions of the various organs rather than to group and classify the various pathologic findings, the gross appearances will be presented with the description of the lesions in the different organs as they were worked out by microscopic study. Before taking up the description of the various organs, attention will be called to the lesions found at necropsy which were not studied with the aid of the microscope. Of these, the most spectacular was the presence of air in the subcutaneous tissues

10. Olitsky, P. K., and Gates, F. L.: Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients, J. Exper. M. **23**:713 (Feb.) 1921.

of the body. This air, during life, first appeared in the subcutaneous tissue of the neck, having passed from the root of the lungs through the loose tissue of the mediastinum. From the neck it extended in some cases over the entire trunk, head and extremities. From a study of the lungs at necropsy and gross sections of them fixed in Kaiserling's fluid, it is felt that the acute interstitial emphysema results from the mechanical rupture of some of the pulmonary alveoli which have become distended by the acute alveolar emphysema which is characteristic of this disease. The air then extends along the interlobular septums and reaches the hilus of the lung through the connective tissue accompanying the blood vessels. Apparently, the connective tissue surrounding the bronchi is more compact and does not furnish a route for the air. From the hilus of the lung the air travels subpleurally over the pericardium and great vessels into the loose tissue of the mediastinum. In this series of twenty-six cases, the subcutaneous emphysema was present in five and emphysema of the mediastinum was found in five more. In these ten cases in which the air had escaped from the alveolar spaces, the influenza bacillus was recovered by culture or demonstrated in sections of the lungs in nine. Although other organisms than the influenza bacillus were present in the lungs in some of these cases, they were not present with sufficient regularity to make the lesions they produced responsible for the escape of the air. From the number of cases in which it was present, the influenza bacillus may well be considered a causative factor in the occurrence of this escape of air, and even if it is only a complicating organism in the epidemic disease, it may be a necessary factor in producing this peculiar lesion. As will be seen later, the pulmonary lesion of alveolar emphysema which leads to the escape of air occurs without the presence of the influenza bacillus, but the alveolar emphysema may not go on to actual rupture of the alveoli and interstitial emphysema formation without the presence of some complicating organism.

The peritoneal cavity was normal in appearance in all twenty-six cases, although in one the appendix was acutely inflamed, so it can be said that the causative factor of the epidemic is not likely to produce a peritonitis.

In this group of twenty-six cases, empyema was present in five, in two of which it was bilateral. No cultures were taken from the pleural cavities in these five cases. The cultures from the lungs and heart's blood and a study of the lung tissues showed both pneumococci and influenza bacilli present, and in one case other bacteria. In five cases, one or both pleural cavities contained a moderate effusion of thin turbid yellow fluid, with evidence of inflammation on the pleural surfaces. Had these patients lived longer, a frank empyema might have developed. In these cases also no cultures were taken from the pleural cavities. In

two of these five cases no influenza bacilli were recovered by culture or seen in the sections of the lungs. The bacteria present in the heart's blood and lungs were the influenza bacillus, streptococcus or another unidentified diplococcus, but they were not consistently present in all cases. From a survey of these cases of empyema and incipient empyema, there is insufficient evidence to permit the designation of any one organism as the cause of the empyema, and as there were always organisms present in the lungs, the pleural condition can hardly be considered due to some unknown virus. That empyema, pronounced or incipient, occurs frequently in these cases (ten out of twenty-six) is a fact, and it presumably is due to several of the complicating organisms.

An acute inflammation of the pericardium was found in only two of the twenty-six cases, and in both instances the pneumococcus was recovered in pure culture, so that it seems fair to rule out the cause of the epidemic as likely to produce a pericarditis.

Involvement of the middle ears or of some of the accessory sinuses to the upper respiratory tract occurred in all the nineteen cases in this series in which the head was opened at necropsy. Of the sinuses, the sphenoidal were involved more often than the others. In three of these nineteen cases, no bacteriologic examination was made on account of the length of time postmortem before necropsy was performed. In the remaining sixteen cases, a variety of bacteria were recovered; but the influenza bacillus predominated being recovered in fifteen of the sixteen cases. The influenza bacillus alone of these bacteria may reasonably be regarded as the causative agent of these infections in the ears and sinuses, if a conclusion is demanded; but, of course, it is well known that various organisms produce empyema of these cavities. The invasion by these organisms, which were recovered by culture, may also have been a secondary one after the tissue had been rendered more vulnerable by some unknown virus. Meningitis was found in only one of the nineteen cases in which the head was opened. In one other, an abscess of the brain was found; and in still another, an encephalitis was suspected. On account of the infrequency of cerebral lesions and as the meningitis was due to the pneumococcus, it seems fair to say that the cause of this epidemic, whatever it may be, is not likely to produce gross cerebral or meningeal lesions.

MICROSCOPIC EXAMINATION

Turning now to the various organs and tissues of the body which were studied microscopically [11] as well as by gross inspection, many interesting and instructive lesions were encountered. One of the first

11. In this study, the sections for microscopic examination were stained with eosin and methylene blue after Zenker's fixation. A few other special stains were also used.

to appear on opening the body was a lesion in the rectus muscle of the abdominal wall. Such a lesion on gross inspection was reported in nine of the twenty-six cases. In fourteen the muscle was reported as normal in appearance, and in three no observation was made on the condition of the muscle. In none of these nine cases in which a lesion of the rectus muscle was noted was a culture made from it. On study under the microscope, however, no organisms were found in eight of the nine cases. In the ninth, a coccus was found in the leukocytes at the site of the lesion. The absence of organisms in the vast majority of the cases makes it seem quite certain that this injury to the muscle was the result of some circulating toxin rather than any organism. In the cases in which the lesion occurred, a variety of organisms were encountered in cultures or sections from the lungs. Of these organisms, the influenza bacillus was most consistently present. If this lesion is a toxic one, it may be the result of some toxin from the influenza bacillus or the unknown virus of the epidemic. No other organism was present in the lungs sufficiently often to be looked on as a specific cause. This lesion in the muscle is similar to the one which has been noted in various acute infections, such as, for example, typhoid fever. As abscesses have been reported in muscles in cases of this epidemic in which the patient survived for some time, it is thought that the appearance of a coccus in the lesion in one of these cases was a secondary invasion, and that this is the explanation of the abscess formation noted clinically in cases of this epidemic by one of us.[12]

The injured muscle in these cases showed, in the gross, a swelling of the muscle fibers with increased friability. In most of the cases, actual hemorrhage had occurred into the muscle substance, separating the muscle bundles and in a few instances extending beyond the muscle into the adjacent subperitoneal tissues of the abdomen and pelvis. On microscopic study, it was worked out that the initial step in this lesion, which in some fibers went on to complete necrosis, was a swelling of the muscle fibers with loss of the striations and loss of nuclei. In other instances, the central part of the fibers apparently became necrotic, but the sarcolemma survived, and evidences of regeneration were shown by an increase of the nuclei. In some fibers, a part showed these degenerative changes, and the remaining part appeared normal. In other fibers, slight changes in the staining reaction of the fibers occurred, but no difference in appearance of the nuclei was observed except that they were more numerous than normal. This was looked on as the slightest perceptible injury to the fiber. The extent of the injury to the individual fibers and the number of fibers involved varied in different cases.

12. Frothingham, C.: Contributions to Medical and Biological Research, Dedicated to Sir William Osler **1**:513, 1919.

Associated with these injuries to the muscle fibers were congestion and actual hemorrhage into the supporting connective tissue of the muscle. As no lesion was detected in the larger blood vessels, it was presumed that the hemorrhage came from the capillaries. If the patient survived, a cellular reaction appeared, consisting chiefly of polymorphonuclear neutrophils and mononuclear phagocytes. These cells invaded the necrotic muscle, surrounded the partially injured fibers and grouped themselves in the interstitial tissue. The polymorphonuclear cells in this exudate became much fewer before many days, and the blood cells from the hemorrhage also soon disappeared. The necrotic muscle was removed by the action of the invading phagocytic cells and probably in part by some enzymatic action without cellular reaction.

Repair of the injured muscle fibers in which the sarcolemma remained was carried on from the sarcolemma from which new fibrils were formed, and eventually a new fiber appeared. In those instances in which a part of the old fiber remained, the new became continuous with it. These new fibers could usually be detected by the fact that with the eosin and methylene blue stain they took the eosin stain less intensely. Also the number of nuclei in the sarcolemma was increased. Gradually the cellular reaction disappeared, and the repaired muscle returned toward its normal appearance, with practically no permanent increase in the supporting connective tissue.

The muscle lesion in these cases was the one that has been described before, and is known as Zenker's degeneration. Usually it does not occur in uncomplicated lobar pneumonia, and therefore its appearance may be of assistance in detecting a pneumonia secondary to this disease in the absence of an epidemic. This muscle lesion, however, has also been noted by MacCallum [13] in streptococcus pneumonia following measles in army camps.

The heart muscle itself seemed to escape demonstrable injury in this epidemic disease. In two instances, the endocardium showed an acute lesion on one of the valves which consisted of a vegetation in which some organization was taking place. The infrequency of this lesion on the endocardium, and the fact that in one instance a pneumococcus was recovered from the heart's blood, makes it seem unlikely that the cause of the epidemic, whether the influenza bacillus or some unknown virus, was responsible for the lesions. In one case, a small area of cellular infiltration, consisting chiefly of mononuclear cells but with a few polymorphonuclear leukocytes and mast cells, was seen in the tissue about a blood vessel in the myocardium; but this isolated observation was not considered to be of any practical importance.

13. MacCallum, W. G.: Monograph No. 10, Rockefeller Institute for Medical Research, 1919.

On gross inspection, the livers in these cases presented no lesions of importance that could be attributed to the causative agent of the epidemic. In one instance, acute congestion was suspected and in another focal necrosis. On microscopic study, several slight lesions were found in some cases. Of these, the most frequently encountered was an infiltration of cells in the connective tissue about the smaller bile ducts. These cells were in most cases entirely mononuclear, but in a few instances polymorphonuclear leukocytes were also present. This cellular reaction was observed in twelve of the twenty-six cases. As it occurred in less than half of the cases, and as this lesion is often encountered in necropsy material from other sources, and as in these cases various bacteria were present, the most that can be said in regard to the cause of the epidemic in relation to this lesion is that it may be one of the various agents responsible for it.

In three of the cases, the parenchymal cells in the midzonal region showed slight changes in their staining reaction in that their cytoplasm stained more purplish with the eosin and methylene blue stain than the other cells, and their nuclei stained a deeper blue and appeared more homogeneous. In this part of the lobule, the red blood cells seemed more numerous in the sinusoids; but there was no cellular reaction or actual necrosis of the parenchymal cells. As this slight lesion occurred in only three cases, it was felt that it had no important relation to the cause of the epidemic. In seven cases, degenerative changes about the central veins (hepatic) of the lobules was seen. This lesion varied from slight vacuolization in the liver cells with slight variation in the staining reaction to actual necrosis of the cells with invasion of the necrotic cells by phagocytes and an increase of leukocytes in the surrounding sinusoids. No organisms were found about these lesions. As this lesion of central necrosis in the liver is quite commonly associated with other infections, and as various bacteria were found in these cases, it is not possible from these few cases to attribute this lesion in this group to any one cause. It may be said that the cause of this epidemic may be another agent which produces central necrosis in the liver.

In this series of cases, the spleens did not present any peculiar lesion nor one that occurred with sufficient frequency to make it apparent that the cause of the epidemic was necessarily responsible. Such lesions as were seen in the gross and microscopically are frequently encountered in the infections with the various types of organisms found in the lungs in these cases. The cause of the epidemic, however, may be another agent which produces these lesions. In the gross one case of congestion, five cases of acute splenitis, one case of infarction, and one case of abscess were described. On microscopic study, a tubercle was found in one of the five cases described as acute splenitis. In the case with abscess of the spleen the infection in the lungs was a

mixed one with a variety of organisms and the microscopic examination of the spleen presented nothing unusual in addition to the abscess. Fibrin at the center of the lymph follicles without pronounced reaction about it except an increase in the polymorphonuclear leukocytes was not infrequently encountered. In a few instances, the red blood cells seemed to have broken out of their capillaries, and in a few others the number of polymorphonuclear leukocytes seemed increased throughout

Fig. 1.—Cortex of suprarenal showing loss of cortical cells in fascicular zone. The disappearance of cells is preceded by disappearance of lipoid material. Low power photomicrograph.

the spleen. The hyaline change in the walls of the small arteries which is so common in the spleen, especially in those dying of acute infection, was frequently seen.

On gross examination the suprarenals were reported normal except in one instance, in which there was a hemorrhage into the substance of the gland, so that no gross lesion can well be ascribed to the cause of the epidemic. On microscopic study, however, a lesion of the cortical cells was observed in sixteen of the twenty-four cases studied. In two

instances, sections from the suprarenal glands were missing. This lesion varied from a simple degeneration of the epithelial cells of the cortex shown by the appearance of vacuoles in the cells and a difference in the staining reaction to actual necrosis of the cells with invasion by phagocytes and a cellular reaction of leukocytes in the surrounding tissues. In the milder cases, repair takes place by the formation of new cells from the adjacent parenchyma, as evidenced by mitoses; but in the more pronounced cases, mononuclear cells invade, and groups of these cells remain in areas from which the gland cells have disappeared and in which there may be some slight increase of connective tissue. This type of lesion in the cortex of the suprarenal is frequently encountered in a variety of acute infections. Its presence in such a large number of these cases makes it seem probable that either the influenza bacillus, which was present so frequently, or some other virus responsible for the epidemic may be another of the causes which produce this lesion in the suprarenal cortex. As no organisms were found in these lesions, it is presumed that they were produced by toxins rather than by the actual presence of an organism.

In the medullary part of the suprarenal gland, in eight instances, there were found small groups of round cells, chiefly of the lymphoid and plasma types. These groups of cells occurred without apparent destruction of the medullary cells or other reason for their appearance. These cell groups in the medullary portion of the suprarenal occur in various conditions, and as they only were found in a third of these cases, it is felt that the lesion bears little relation of importance to the cause of the epidemic, which, however, may possibly be another of the factors responsible for their production.

The kidneys presented no lesions of importance on gross inspection in this series. In eight of the twenty-four cases studied (in two instances no sections of the kidneys were preserved) a microscopic lesion was seen. Of these eight cases, two showed simply areas of cellular infiltration consisting of lymphoid cells and polymorphonuclear leukocytes scattered at irregular intervals throughout the kidney substance. The cause of these groups of cells was not apparent, nor was it evident that any damage of importance had occurred in the renal tissue. In the other six cases, a definite glomerular lesion was present which consisted of a proliferation of the endothelial cells lining the glomerular capillaries and an increase in the number of polymorphonuclear leukocytes in the glomerular tufts. In some instances, there was also an increase in lymphoid cells and polymorphonuclear leukocytes about the capsule and among the tubules, which suggested that the toxic lesion had in some instances injured the epithelium of some of the tubules and called forth slight cellular reaction. In one instance,

in a patient who survived for nearly five weeks, the capillary walls of the tufts were somewhat thickened, which was looked on as possibly the end result of this acute lesion.

No bacteria were found in any of these lesions, and it was felt that it was a toxic one. Such a lesion occurs in a variety of acute infections produced by the organisms present in these six cases, so that the cause of the epidemic, whether the influenza bacillus or some other virus, could only be looked on as possibly another agent capable of producing this acute glomerular lesion.

In the pancreases in this series of cases, no abnormalities were described in the gross, and on microscopic examination no lesions of importance were found, so that it may be said that the cause of the epidemic does not produce a demonstrable lesion in the pancreas.

On gross inspection, the gastro-intestinal tract showed a variety of slight lesions, but not one with sufficient frequency to make it seem likely that it bore any special relation to the causative agent of the epidemic, especially as the lesions seen are known to occur in various acute infections produced by the bacteria present in these cases. In one instance, acute appendicitis was present. In one case, injected areas were seen in the cecum and ileum; in another, congestion of the gastric mucosa; and in two others, actual hemorrhagic spots in the stomach wall. In one instance, actual hemorrhage had occurred into the lumen of the stomach; and in one case with emphysema of the mediastinum, an air bubble was found in the wall of the stomach toward the cardiac end. On microscopic study of the gastro-intestinal tract, which was carried out on only ten cases, no distinctive lesions were found. In several instances, lesions such as are found in acute infectious diseases were seen, such as thrombosis in small vessels, punctate hemorrhages, small areas of cellular reaction and migration of polymorphonuclear leukocytes toward the lumen of the intestine; but on account of the infrequency of these lesions and their occurrence in other infections they apparently were of no importance in relation to the cause of the epidemic.

The testicles in these cases presented, on microscopic study, an interesting lesion which occurred with sufficient frequency to make it seem associated with the cause of the epidemic or the most frequent complicating organism, namely, the influenza bacillus, especially so as the lesion is not ordinarily encountered in acute infections produced by the other complicating organisms found in these cases. The early stages of this testicular lesion, however, have been described adequately by Mills [14] in cases of pneumonia following measles as well as in cases

14. Mills, R. G.: The Pathological Changes in the Testes in Epidemic Influenza, J. Exper. M. **30**:505 (July) 1919.

of influenzal pneumonia. In the cases in which this lesion occurred, the influenza bacillus was always present, so that no decision can be reached as to whether the influenza bacillus or the virus of the epidemic, if they are separate, is the cause of this injury to the testicle.

Gross inspection of the testicle and the threading of the tubules failed to disclose this lesion, because in only one of the twelve cases in which the lesion occurred was anything abnormal reported in the

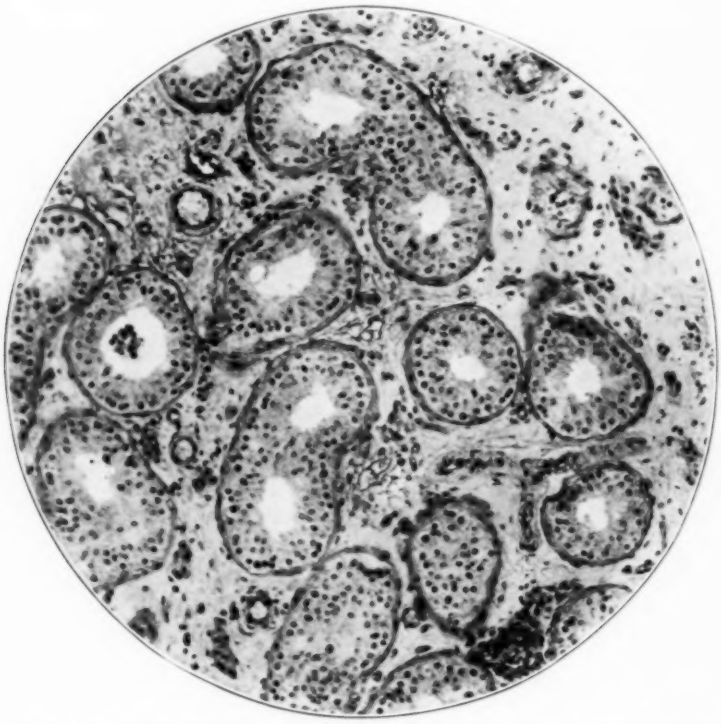

Fig. 2.—Testicle showing aspermia, thickening of basement membrane and edema of the interstitial tissue. Low power photomicrograph.

gross; and, furthermore, in one other in which interstitial orchitis was reported from the gross study, the testicle appeared normal under the microscope.

Unfortunately microscopic study of the testicles was only carried out in seventeen of the cases, but in twelve of these the special lesion was found in them in some degree. It was possible to follow the lesion from its start to the end result in these twelve cases. No organisms

were found in the sections, so it is presumed that the lesion was a toxic one. The primary disturbance was a degeneration of the epithelial cells of the tubules as evidenced by loss of the cell outline, especially in the deeper layers and pycknosis of the nuclei. Evidence of mitosis disappeared and the epithelium separated as a whole from the underlying basement membrane. In some instances, edema in the interstitial tissue was present. If mild, this lesion was unassociated with cellular reaction; but if extensive and severe, a moderate cellular reaction of lymphoid cells, polymorphonuclear leukocytes and mast cells occurred in the connective tissue framework for the tubules. The interstitial cells of the testicle seemed to be unaffected by this process.

Soon after the degeneration and desquamation of the epithelial cells, a deposit of hyalin collagen with nuclei in it appeared on the gland side of the basement membrane and extended out into the mass of injured epithelial cells in places. In the more severe cases, this material was so extensive that it left the tubules in the later stages entirely sclerosed, as this hyaline material eventually seemed to change into definite connective tissue. In the milder cases, the sclerosis of the tubules was only partial. The basement membrane of the tubules became thickened as the process healed. No evidence of regeneration of the epithelium of the tubules was made out, and it is a question as to how well these tubules would have functioned again had the patients lived. In some instances, after healing there seemed to be an increase in the interstitial connective tissue.

The aortae in these cases were reported as normal on gross inspection in eight of the twenty-six cases. In one instance, lesions suggesting syphilitic aortitis were found, and in the remaining seventeen cases, mild involvement of the intima with typical early arteriosclerotic changes occurred. On microscopic study of the aortae the intimal lesion was usually the one found in a variety of conditions consisting in a cellular invasion chiefly of mononuclear cells, often laden with fat, and occasionally a polymorphonuclear leukocyte, together with a slight fibrous thickening of the intima. There was nothing peculiar to the lesion in these cases; and if it was due to the cause of the epidemic, it simply means that this is another one of the many agents which produce this arterial change.

EXAMINATION OF THE LUNGS

The lungs in each case in this series presented both gross and microscopic lesions. Considerable confusion has been created in regard to the gross and microscopic lesions due to this epidemic disease, because the pathologists who have reported on the pulmonary lesions have not always endeavored to separate the lesions due to the virus

of the epidemic and those dependent on the complicating organisms. On account of the variety of complicating organisms, manifold gross pathologic appearances have been described, and a sharp separation between the lesions produced by the virus of the epidemic disease and the complicating organisms has not been made.

Fig. 3.—Cut surface of a hardened influenza lung, showing the pathologic condition of the uncomplicated virus lesion, namely, acute alveolar emphysema and hemorrhagic exudate. A portion of the pleura is included and shows the dusky red mottling which accompanies this lesion.

In forming an opinion in regard to the lesions produced by the virus of the epidemic, the study of these cases from Camp Devens has been supplemented by some material from the Peter Bent Brigham Hospital, and an analysis of the published studies on influenzal pneu-

Fig. 4.—Appearance of virus lesions in lung followed by influenzal bronchitis, peribronchitis and bronchopneumonia. There is marked alveolar emphysema and interstitial emphysema, and the dissection of air toward the hilus of the lung is shown.

monia mentioned above. All of the workers in this field have recognized lesions occurring early in the lung involvement which are not present in cases of lobar and bronchopneumonia unassociated with this epidemic disease. It is felt that it is now possible to pick out and arrange in sequence the lesions produced by the virus of the epidemic disease and

Fig. 5.—A tangential section through a hardened lung, showing alveolar emphysema, bronchitis and peribronchitis and marked thickening of interlobular septums. There are a few bronchiectatic cavities at both ends of the section.

follow the course of these lesions even in the presence of those produced by complicating organisms.

The lesions peculiar to the virus of the epidemic and their relation to the different bacteria and other pathologic processes will be described

in detail later. In general, the lesion consists of an alveolar emphysema with an accompanying hemorrhagic exudate, in some instances interstitial emphysema, and the formation of a hyaline membrane in the alveoli and the alveolar ducts.

On gross inspection in the earliest fatal cases, partially collapsed lax lungs were seen which on section presented wet deep red surfaces

Fig. 6.—Two sections from an influenzal pneumonia case followed by pneumococcus lobular pneumonia. The effects of the virus lesion are shown by the alveolar emphysema and the interstitial emphysema. The arrows point to the bullae of interstitial emphysema. Slightly reduced.

yielding a blood tinged serous liquid from some areas and deep red liquid of the consistency of blood from others. On close inspection, especially when the cut surfaces were washed, the air-containing portions were found to be coarser in texture than the normal lung, owing

to the presence of dilated air spaces. Also in some instances air vesicles were visible beneath the pleural surface and along the supporting tissue of the lungs. This picture was not uniformly distributed throughout the lungs but was limited in some cases to certain of the lobes.

This gross appearance of the lungs, which was considered to be due to the virus of the disease, was quickly complicated by the lesions of different bacteria, and in the gross more than microscopically in some instances the characteristic features of the virus lesions were obscured by the superimposed reactions.

Thus, even in the early stages, the hemolytic streptococcus infection would mask to a considerable degree the lesions due to the virus of

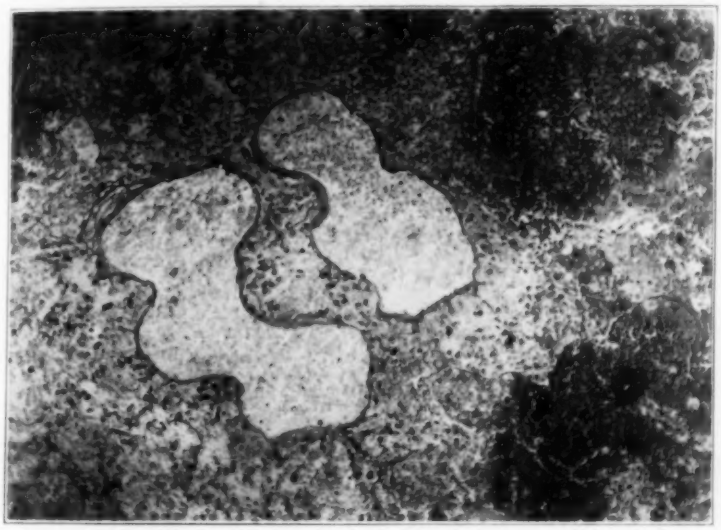

Fig. 7.—Low power photomicrograph illustrating the uncomplicated virus lesion of influenza in the lung, acute alveolar emphysema, hyaline membrane and hemorrhagic exudate.

the epidemic disease. It is noteworthy that this streptococcus was a predominating secondary invader in some localities and that it invaded the lungs early. The pneumococcus infections presented the characteristic consolidations due to this organism, which were either lobular, lobar or patchy in distribution. The staphylococcus infections caused multiple abscesses. The influenza bacillus was frequently present in abundant numbers without masking the virus lesion. Also the influenza bacillus produced in these cases and maintained a definite type of bronchitis, bronchiectasis, and peribronchitis after the initial virus lesion had subsided. In these cases, the smaller bronchi were promi-

nent on cut section, and their dilatation was apparent. These peribronchial lesions at times were so extensive that they coalesced and made the whole lung practically solidified.

These various types of consolidation and bronchial lesions became more pronounced and the typical virus lesion became less evident in cases in which the patient survived a week or more after the extension of the disease into the lungs. As MacCallum [5] has emphasized, it is

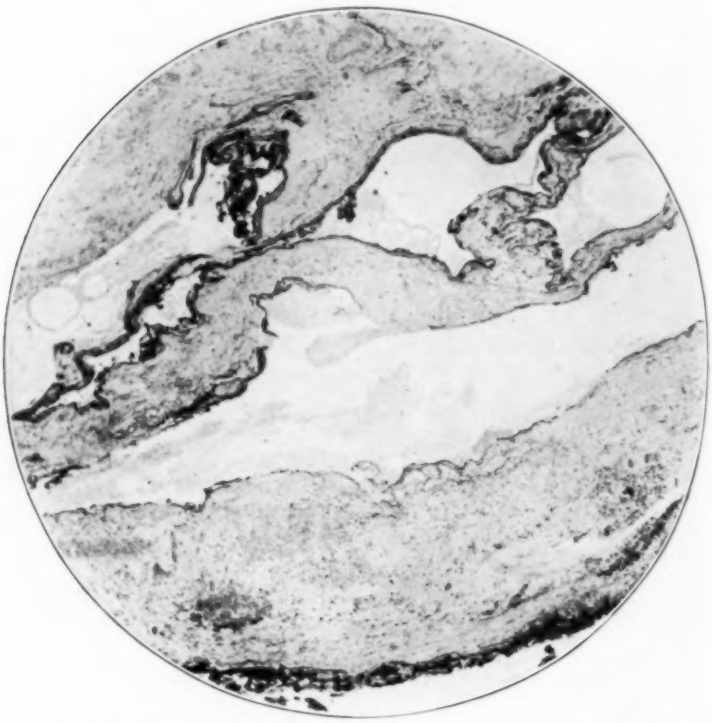

Fig. 8.—Section from the mediastinum. Interstitial emphysema in a case of pneumococcus mediastinitis. Note that the spaces occupied by air are lined with a hyaline membrane similar in appearance and staining reaction to the hyaline membrane found in the acute alveolar emphysema of the lungs in uncomplicated influenzal pneumonia. Low power photomicrograph, about 120 diameters.

possible to pick out in the gross the lesions due to the streptococcus the staphylococcus as described by Chickering,[15] the pneumococcus and

15. Chickering, H. T., and Park, J. H.: Staphylococcus Aureus Pneumonia, J. A. M. A. **72**:617 (March 1) 1919.

the influenza bacillus. In different lobes of the lung in one person a different gross appearance was at times encountered, because the secondary invading organisms varied.

In each of these cases from the Camp Devens series organisms were recovered by cultures or found on microscopic examination of sections of the lung. In some of the early cases in which organisms were only found in the sections, the distribution of them was in the bronchi and

Fig. 9.—Low power photomicrograph of the virus lesion and an early bacillus influenzal bronchopneumonia, the former indicated by the acute alveolar emphysema and hyaline membrane, the latter by the infiltration with polymorphonuclear leukocytes.

not in the alveolar regions. Of the various organisms found, the influenza bacillus was seen much more frequently than other organisms, such as the pneumococcus and the streptococcus. It was found in twenty-two of the twenty-six cases. In a few of the cases in which death occurred after a relatively short time, from seven to ten days

from the start of the epidemic disease, the influenza bacillus was not recovered by culture or seen in sections of the lung.

In all but one of these cases (the exception being the patient who survived over four weeks) the peculiar pulmonary lesion mentioned above was present. It was felt, however, that this lesion was not produced by any of the bacteria present since this lesion was found in one early case in which the only bacterium present was an unidentified coccus found in the stained sections in the bronchial exudate. Also, in two other early cases in which the pneumococcus with the usual pneu-

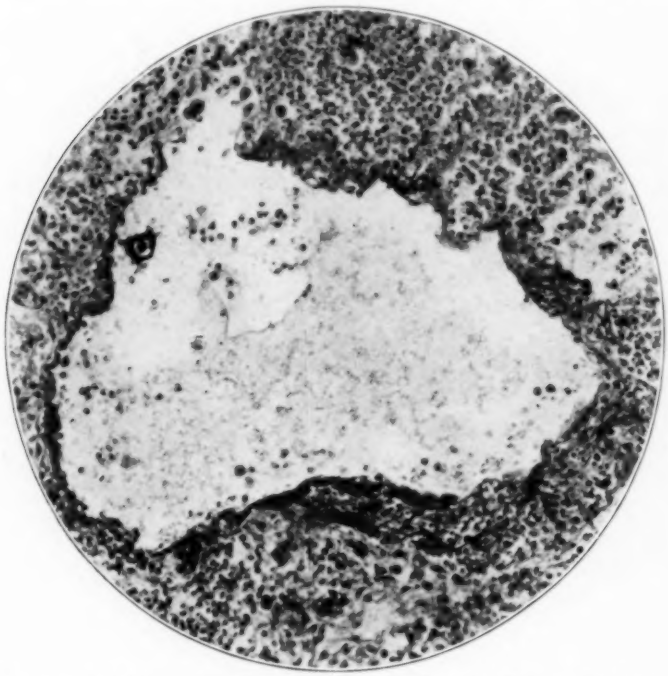

Fig. 10.—A higher power photomicrograph of field in Figure 9 to show the polymorphonuclear leukocyte exudate as a result of the Bacillus influenzae infection.

mococcus lesions was the only organism present in the lungs, this peculiar lesion was present in its early stages. Thus, in three cases in which the influenza bacillus was not present this characteristic lesion was found, which is strong evidence against the influenza bacillus or its toxin being the cause of this lesion. No other organism was found in even a majority of the cases, so that it is not reasonable to consider these other bacteria encountered in this group as the cause of this pulmonary lesion.

In a detailed description of the different processes in the lungs it is important to keep in mind the difference between the pulmonary lesion peculiar to the virus of the epidemic and the various lesions produced by the secondary invading organisms. For convenience, the lesion due to the virus of the epidemic disease will be called the virus lesion in the following description. In order to simplify the description, an outline of the development and repair of this virus lesion will be given

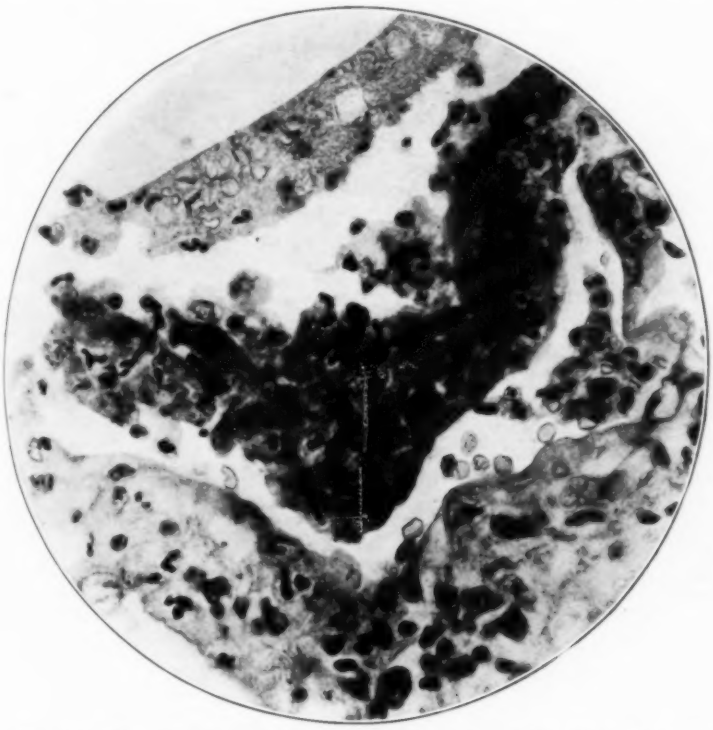

Fig. 11.—Photomicrograph about 700 diameters illustrating the early repair of a hyaline membrane, namely, the invasion with polymorphonuclear leukocytes and macrophages.

as it was seen on microscopic study of the lungs. As secondary infection was present in each instance, it is not possible to decide whether certain of the existing pathologic processes would have occurred had the virus lesion remained uncomplicated. The earliest death in this series occurred seven days after the onset of the epidemic disease and the latest thirty-two days after the onset.

The virus lesion at the start consisted in an injury to the epithelial cells of the smaller bronchi, the bronchioles, the alveolar ducts and the lining of the alveoli themselves, desquamation of this epithelium and disappearance of it. In some places considerable strips of desquamated epithelium were seen detached from the basement membrane but still preserving a normal staining reaction. At the same time, there was intense congestion of the blood vessels in these areas, and although no

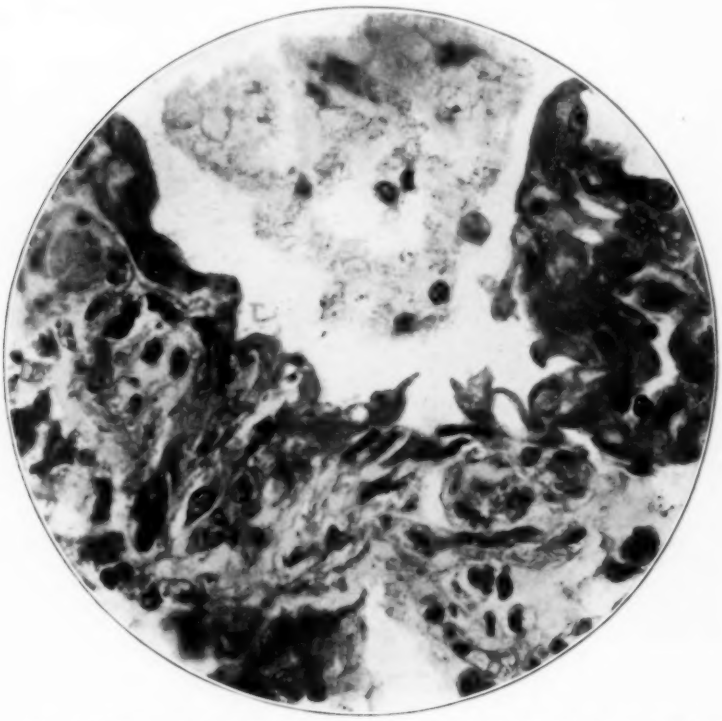

Fig. 12.—Photomicrograph of the virus lesion, about 700 diameters, showing a later stage in the repair of the virus lesion of the lung. The organization of the hyaline membrane is evidenced by the ingrowth of fibroblasts.

actual injury to the blood vessels could be made out, there must have been an injury because the red blood cells had broken out into the lumen of the bronchial tree and the alveolar spaces and a slight amount of fibrin had been deposited. In addition, a hyaline-like membrane was found in the alveolar spaces. This membrane outlined cell-free spaces presumably occupied in life by air. In places, the membrane was closely applied to the walls of the alveolar ducts and alveoli and

sometimes appeared to have replaced the walls. In other places, desquamated epithelial cells or red blood cells and leukocytes lay between the hyaline membrane and duct or alveolar walls. In general, the arrangement and outline of this hyaline material suggested that its position was an effect of air forced into exudate. Of just what this hyaline membrane was composed was not determined, but apparently it was related to the action of the air and virus on some of the body fluid or exudates in this particular disease and not, as some claim, to the degenerated epithelium, because in two cases in which the air had escaped from the lungs this same hyaline membrane was found in the

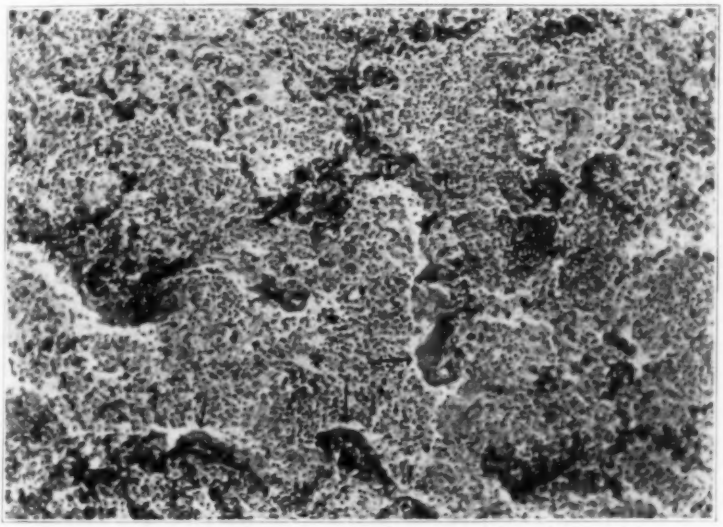

Fig. 13.—Low power photomicrograph of a lung with a virus lesion of influenza with a superimposed pneumococcus lobar pneumonia. The arrows point to hyaline membrane. The fibrinopurulent character of the exudate is shown. From our series of cases, the complete filling of emphysematous alveoli and alveolar ducts with exudate is brought about only by pneumococcus infection.

tissues of the mediastinum where no epithelium existed. In both of these cases, there was a pneumococcus pericarditis and an acute puriform infiltration of the fat and areolar tissue of the mediastinum. There was also a penetration of air bubbles into the mediastinal tissues and wherever the air came in contact with this exudate, the hyaline membrane was found. It is felt that for the formation of this membrane the air must be under some tension in its contact with the exudate.

In addition to the peculiar changes mentioned above, the alveolar spaces were in many instances markedly distended with air, so that adjacent lung tissue was compressed. Just what caused this distention was not evident, but it was assumed that the hemorrhage and hyaline material in some way acted as an obstruction to the outflow of air without preventing so effectively the inflow. In some instances, these alveoli were so distended that rupture occurred in the wall, and the

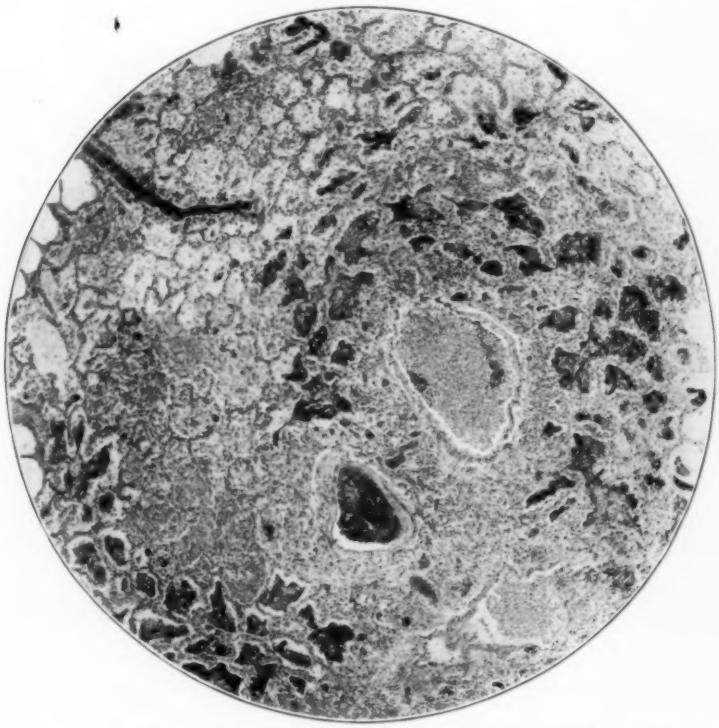

Fig. 14.—Low power photomicrograph of influenzal pneumonia followed by bronchitis and peribronchitis. The interstitial pneumonia and the fibrinous exudate into surrounding alveoli is well shown.

air extended into the adjacent connective tissue framework of the lung. As no extensive injury to the alveolar walls was seen in these cases, it was felt that the rupture of the air was purely mechanical.

In the early cases, few leukocytes or phagocytes were present with these various lesions, and it is not clear just what the next step in this reaction would have been had it remained uncomplicated. However, in all the cases in this group other organisms secondarily invaded the

lungs. The reaction associated with the secondary invading organism varied somewhat with the organism, and the different processes seen will be discussed below. First, however, the process of repair of the virus lesion will be considered. The hemorrhage was cleared up by the taking up of the red blood cells by endothelial phagocytes, as cells of this type filled with red blood cells were seen. The epithelial lining of the bronchial tree and the alveolar spaces regenerates, as was evident

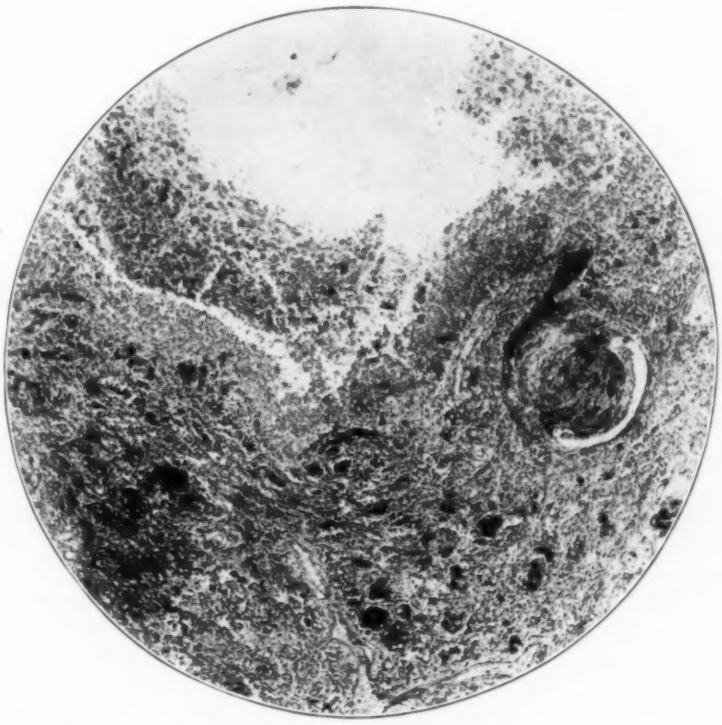

Fig. 15.—Low power photomicrograph of a portion of a bronchiectatic abscess, presumably the result of Bacillus influenzae infection. A vein with a large thrombus undergoing organization is shown on the right of the abscess wall.

from the appearance of mitosis in the epithelial cells and the presence of newly formed groups of epithelial cells which had not assumed the usual appearance of the older ones. The hyaline membrane was quite resistant to the action of phagocytes or ferments, as it persisted apparently unchanged after the repair of the other elements of the virus lesion had begun. In the later cases, this hyaline membrane was

invaded by leukocytes and phagocytes and eventually organization with connective tissue took place into it. If some of this hyaline membrane had been removed by ferment action, no evidence of it was seen in these cases, but it seems reasonable to consider that such action may have been going on as well as the phagocytosis and organization. The emphysema of the alveolar spaces persisted to some extent in the patient who survived, but this lesion was more pronounced in the early days of the pulmonary involvement. Although frequently in the later stages the alveoli were distended, they usually were filled with exudate owing to the secondary invading organisms.

In one case an interesting condition was encountered in that in one part of the lung the old virus lesion was undergoing repair amid the lesions produced by secondary invading organisms, and in another part of the lung an early fresh virus lesion was found with all the usual histologic findings. This also has been observed by Goodpasture.[2]

Returning now to the actual processes going on in the lung owing not only to the virus of the epidemic disease but to the secondary invading organisms, a complicated pathologic picture was presented. The character of the lesions varied with the organisms found in the lung; thus, the pneumococcus superimposed the usual picture of a lobar pneumonia on this virus lesion, and if the virus lesion was not present in the particular lobe, there was the appearance of a straight lobar pneumonia. In the same way, in another case the hemolytic streptococcus produced its usual picture in the lungs in addition to the virus lesion. In other cases various unidentified organisms had invaded the lungs and produced local abscesses and even extensive gangrene. The details of the various lesions will not be discussed in this report, because they add nothing new to the existing knowledge of the pathology of such processes.

The invasion of the lung with the influenza bacillus, however, presented a pretty definite picture of interest, especially as it is possible that the virus lesion may eventually be attributed to this organism, and therefore what is about to be described may be simply additional processes due to the same cause. The exudative and infiltrative lesions considered to be produced by the influenza bacillus were not peculiar to that organism, as similar lesions have occurred in bronchopneumonia from the streptococcus and other causes.

In the smaller bronchi exudate was found consisting of polymorphonuclear and mononuclear leukocytes, in addition to red blood cells. These leukocytes were apparently attracted to the lumen of the bronchi by the bacteria or some toxin such as influenza bacilli and other organisms were found both free and intracellular in the lumen of these small bronchi. The process extended laterally from the lumina of the bronchi into their walls and involved not only the adjacent

tissue, but also the surrounding alveoli. The process consisted in congestion of the blood vessels with hemorrhage and the deposition of fibrin, necrosis of the epithelium lining of the alveoli and the presence of an inflammatory exudate through the supporting tissue and in the air spaces. This peribronchitis was seen in parts of the lung in which the virus lesion was not present, as well as being superimposed on the

Fig. 16.—Photograph, about one-half the natural size, of a late stage of repair in influenzal pneumonia, in which the virus lesion has been followed by Bacillus influenzae, bronchitis, peribronchitis and bronchopneumonia. The alveolar emphysema persists. To be noted are bronchiectases of a large size completely surrounded in the middle portion of the figure by sclerosed lung tissue. The white patch at the apex shows an earlier stage of organization. The permanent character of the bronchiectases is particularly well illustrated in this photograph in the middle portion of the figure.

virus lesion, and therefore was considered to be due to the influenza bacillus or some other organism irrespective of the virus. As this process extended laterally, blood vessels and lymphatics became involved. An acute inflammatory reaction in the arterial walls was seen in some cases with a fibrin deposit, necrosis of the walls of the vessel and cellular infiltration. Thrombosis was found in the blood vessels, and the lymphatics were distended with various types of

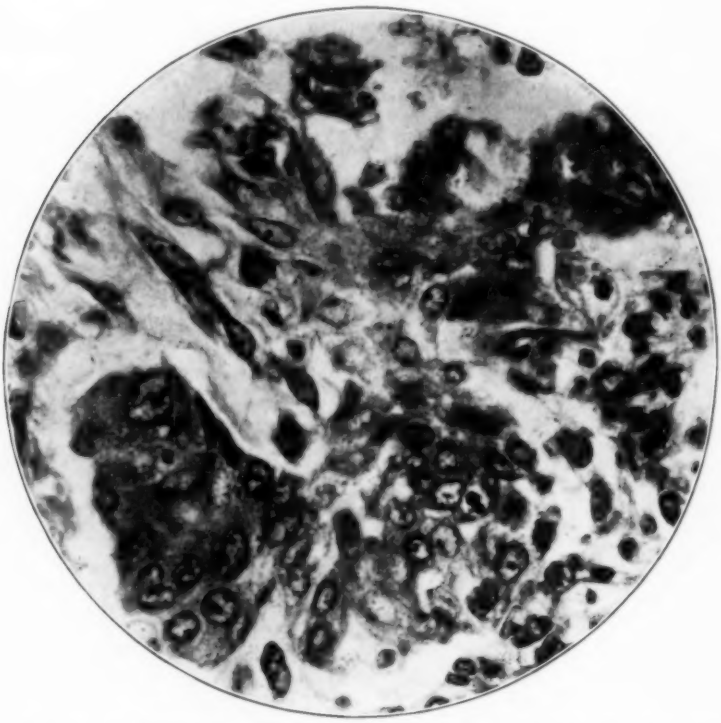

Fig. 17.—Photomicrograph of about 700 diameters showing the excessive regeneration of epithelium in atelectatic alveoli in the repair of the virus lesion. This epithelial regeneration is an almost invariable accompaniment of repair when organization occurs.

leukocytes and phagocytic cells. This thrombosis in the blood vessels in the peribronchial lesions plays an important part in the fate of the exudate in the parts of the lung supplied by these vessels and probably accounts for the necrosis and organization which was often seen.

In these lesions, hemorrhage was a conspicuous factor, and even as the lesion began to repair evidence of fresh hemorrhage was frequently found. It was felt that these red cells broke out of the vessels as part of the lesion about the bronchi and were not just the hemorrhage that remained from the virus lesion. It was one of the interesting features of these lungs that along with the process of repair the acute process was still actively going on. With this acute inflammatory reaction in and about the bronchi, the lumen of the bronchi often became dilated, and this dilatation of the bronchi in some instances remained after repair had taken place, and a condition of chronic bronchiectasis resulted.

As early as the twelfth or thirteenth day after the onset of the epidemic disease, evidence of repair of this bronchitis and peribronchitis began to appear. The epithelium in the bronchi and alveolar walls regenerated. Organization took place into the fibrin in the alveolar spaces and wherever it was deposited. Organization also occurred in the lymphatics and in the thrombosed vessels. There was nothing special in regard to the character of the organization. In some of the later cases certain of the smaller bronchioles were seen with a fresh epithelial covering over the underlying new connective tissue and the bronchiole permanently enlarged.

In summarizing the description of the lung lesions one may say that in the lungs on gross inspection the hemorrhagic appearance of the cut surface, the alveolar emphysema and in some instances the interstitial emphysema demonstrated the presence of the virus lesion. Dilated and prominent bronchi with a confluent bronchopneumonia emphasized the presence of the influenza bacillus lesion superimposed. Variable pictures of lobar pneumonia, patchy pneumonia, abscesses and gangrene showed that other organisms of various sorts were present. These findings were confined to one lobe or scattered throughout, or, as appeared in one case, various lesions appeared in the different lobes. Microscopically, the virus lesion could be separated from the lesions produced by other organisms and followed through its various phases. In addition, the inflammatory reaction to the influenza bacillus formed a fairly characteristic picture, and the picture produced by other organisms such as the pneumococcus and the streptococcus was as it usually is found.

Tissue from higher up in the respiratory tract was not preserved in many of the cases, but in those in which sections of the larger bronchi and trachea were studied the process was one of injury and desquamation to the epithelium with congestion and cellular reaction in the subepithelial layer and connective tissue. In some instances, the invading cells were polymorphonuclear leukocytes, in other mononuclear cells of the lymphocytic series.

CONCLUSIONS

From this study we have drawn the following conclusions: The cause of the influenza epidemic has not been established. The influenza bacillus is one of the secondary invading organisms. The virus which causes the epidemic, in addition to the general febrile reaction, the general toxic symptoms and involvement of the upper respiratory tract, produces in the lungs in a certain percentage of the cases characteristic lesions which we believe are pathognomonic of this disease.

The hyaline membrane in alveolar ducts and alveoli of the lungs is an effect produced by air forced into exudate.

The virus which produces the epidemic may also be responsible for Zenker's degeneration in muscle, a degenerative lesion in the cortex of the suprarenal gland and an injury to the tubules of the testicle, but we cannot exclude the effect of the influenza bacillus as a contributing factor in the production of these lesions.

All cases which terminated fatally were complicated by invasion with bacteria of which the influenza bacillus was the most frequent so that it is impossible to decide what the course of the virus lesion would have been if uncomplicated.

The pulmonary lesion due to the virus of the epidemic can be detected in the presence of superimposed secondary pulmonary infections.

The alveolar emphysema leads to rupture of the alveoli, interstitial emphysema, and finally escape of air into the subcutaneous tissues of the body. It is not established whether this would happen without secondary infection.

The pneumococcus and streptococcus produced in the lungs in the presence of the virus lesion their usual pathologic picture. *Bacillus influenzae* in these cases was responsible for the production and maintenance of a characteristic combination of bronchitis, peribronchitis, bronchiectasis, and bronchopneumonia.

OBSERVATIONS ON CHANGES IN THE SIZE AND SHAPE OF HEARTS DURING THE PROGRESS OF COMPENSATION *

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The general impression prevails that considerable variation in heart size is a not infrequent occurrence in pathologic conditions, and that such variations are indicated by variation in position of the apex beat due to left ventricular involvement. This, however, is not borne out by the few definite statements which could be found in the literature. Mackenzie states that during the progress of compensation no appreciable difference in heart size could be detected. Hoffman [1] states that in chronic heart disease compensation may or may not be accompanied by change in size and that size in itself is no certain indication of functional capacity, that being determined by muscle tonus. Martin [2] cites a case in which teleoroentgenograms during the convalescence from pneumonia showed a diminution in size of the heart. Vaquez [3] illustrates a case of myocarditis showing progressive retraction of all borders during intravenous injections of strophanthin. However, the extent of such changes is not indicated except in Vaquez' case, in which it amounted to 2.7 cm. It was this lack of exact data that prompted us to make this study.

The differences of opinion on this subject are probably partly due to the large personal factor in the percussion of heart borders. It was decided, therefore, to percuss the heart outlines of patients with decompensated chronic lesions at various times during their stay in the hospital, note the borders so obtained with lead markers, and control such determinations by teleoroentgenograms in order that the percussion errors might be visualized and more exact data of the heart size obtained. In the examination of roentgen-ray films, two main points were determined: First, the so-called transverse diameter of the heart; and, second, the heart outline. The transverse diameter is usually defined as the sum of the greatest distance of the right and left borders from the median line, commonly designated *ML* and *MR*. It seems to be well established that this diameter taken in conjunction with the

* From the Investigative Service, Medical Department, Michael Reese Hospital.

1. Hoffman: Erkrankungen des Herzens, 1911, p. 277.
2. Martin: Am. Jour. Rontgenol. **8**:295, 1921.
3. Vaquez and Bordet: Heart and Aorta, translated by Albert Honeij and John Macy, Yale University Press, 1920, p. 63.

heart outlines furnishes the most reliable evidence as to changes in heart size. It is also of value to determine the diameter in the second or third interspace.

In all twenty-one cases of decompensated chronic endo- and myocarditis were observed during one or more periods in the hospital. Of these, eleven patients had mitral lesions; one, aortic insufficiency, and nine, myocarditis. These cases all presented the usual clinical features of failure of the right side of the heart occasionally combined with failure of the left side of the heart. For purposes of comparison they were further divided into three groups:

(*a*) Those leaving the hospital unimproved and whose heart outlines remained unchanged.

(*b*) Those leaving the hospital with hearts more or less compensated, with heart outlines unchanged.

(*c*) Those leaving the hospital improved and with heart outlines changed.

Under group (*a*) (Table 1) were four cases, three of primary myocarditis and one of primary mitral lesion. As stated above, successive roentgen-ray plates of these patients superimposed on each other showed practically identical outlines in spite of variations in the transverse diameters up to 1 cm. The table shows also that, in the main, percussion figures and roentgen-ray measurements agreed fairly well, there being a difference of from 0.7 cm. to 1.6 cm. between the two; as a rule, the percussion figures were the lower. There is, however, one striking exception. This was in the case of R. R., in whom on entrance the transverse diameter, according to percussion, was 23.5 cm. and the roentgen-ray measurement 18.9 cm. Had there been no control of percussion here, this would have been looked on as a case of marked diminution in size of the right side of the heart. It is well to note here the possible errors involved in determining slight changes in heart size by percussion alone. First, as to the right border: In using the lightest or threshold percussion, one often finds especially in decompensated hearts a change of note, that is, a rise in pitch, about 1.5 cm. to the right of the true heart border, when percussing from without toward the heart border. This is indicated in Figure 1 by the outer of the two lead markers. This change in note often coincides with a dense hilus shadow. In order to determine the real heart border, one must continue the percussion until the change of note is accompanied by a feeling of resistance in the pleximeter finger tip. This is indicated in the illustration by the second marker. As the maximum retraction of the right border in our roentgen-ray controlled cases was 2.5 cm., it can be seen of what great importance this single error may be. The left border can, of course, be determined best by the position of the apex beat. However, the apex beat as determined by palpation

is not always coincident with the apex as determined by the roentgenogram. This difference is present when the heart has become enlarged sufficiently to reach the lateral chest wall posterior to the anterior angle of the ribs. Here the marker will always lie outside the roentgen-ray position of the apex by a distance equal to the thickness of the chest wall, a considerable distance in fat or muscular people (Fig. 6, seventh left interspace). Moreover, if the heart enlarges beyond this point, the apex can no longer move outward, since it has already reached the lateral chest wall and must therefore move backward and lie

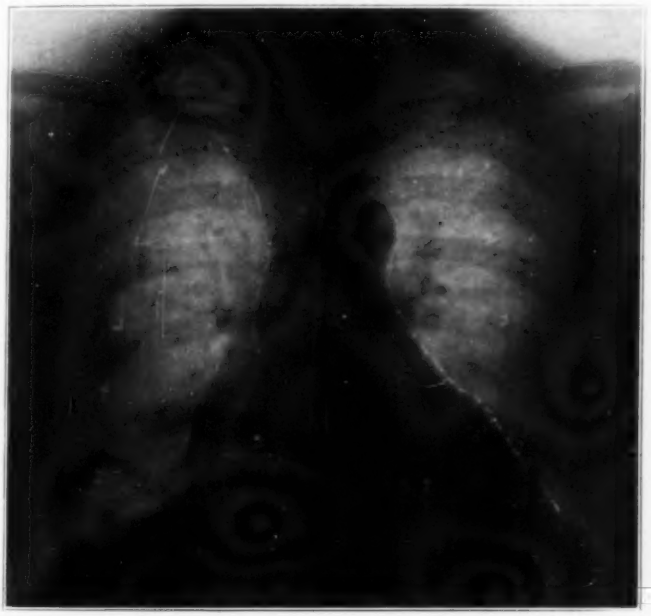

Fig. 1 (H. B., Table 3).—Markers showing sources of error in percussing right heart border.

obliquely in the chest cavity. When this occurs, an anteroposterior distance plate, being simply a projection of this obliquely placed heart, must have a somewhat smaller transverse diameter than the heart itself. Both methods then are liable to error in greatly enlarged hearts.

Group B (Table 2) includes those patients who left the hospital with hearts more or less compensated, but with the heart outlines the same as on entrance. This included seven cases, three of which are also classed in Group (*c*) on different admissions. There was one diagnosed myocarditis and six mitral lesions. The improvement in

TABLE 1.—*Patients Leaving Hospital Unimproved with Heart Outlines Unchanged*

Name	Age	Lesion	Decompensation	Improvement	Dates	Cardiothoracic Ratio	Percussion Measure			Roentgen-Ray Measurements			Urine, C.c.	Pulse	Remarks
							Right	Left	Total	Right	Left	Total			
D. F.	57	Myocarditis, hypertension and heart block	No	.....	10/16/22 10/30/22	0.56	3 4	11 11.5	= 14 = 15.5	4 5.1	10.2 9.7	= 14.2 = 14.8	...	.....	Considerable haziness in lungs in first plate, second much clearer
R. R.	53	Myocarditis, aortitis, hypertension, electrocardiogram showed slight arborization block	Yes	No	11/25/22 12/12/22 1/18/23	0.71	9.0 5.4 6.0	14.5 12.6 13.7	= 23.5 = 18.0 = 19.7	5.7 6.5 7.4	13.2 12.2 10.5	= 18.9 = 18.7 = 17.9	660	100–114 80	No change
L. H.	48	Myocarditis and fibrillation	Marked	Very slight	9/ 8/22 10/24/22	0.69	5.0 5.8	16.0 14.7	= 21.0 = 20.5	6.5 5.5	12.2 12.2	= 18.7 = 17.7	...	.....	No changes except in the region of conus pulmonalis
M. C.	46	Double mitral auricular fibrillation	Yes	No	10/17/22 11/ 6/22 11/22/22	0.66	5.5 4.0 4.5	11 11 11.5	= 16.5 = 15.0 = 16.0	6.0 4.7 7.5	10.4 11.9 9.8	= 16.4 = 16.6 = 17.3	700 750+ —	90 irreg. 60-84 irreg. 60 irreg.	No change

subjective symptoms was marked. Objectively, there was diminution of dyspnea and of cyanosis, somewhat lessened liver swelling and edema, in some marked slowing of the pulse and in two cases a change from fibrillation to sinus rhythm. Functionally, however, the improvement was only moderate, and one patient returned to the hospital in a short time with decompensation. The heart outlines in the patient with myocarditis are reproduced in Figure 2 (C. H. Table 2). This case was included in the group despite the fact that there was a slight change in heart outlines, for reasons given later. The technic used in obtaining the composite plates in the illustrations was to superimpose different

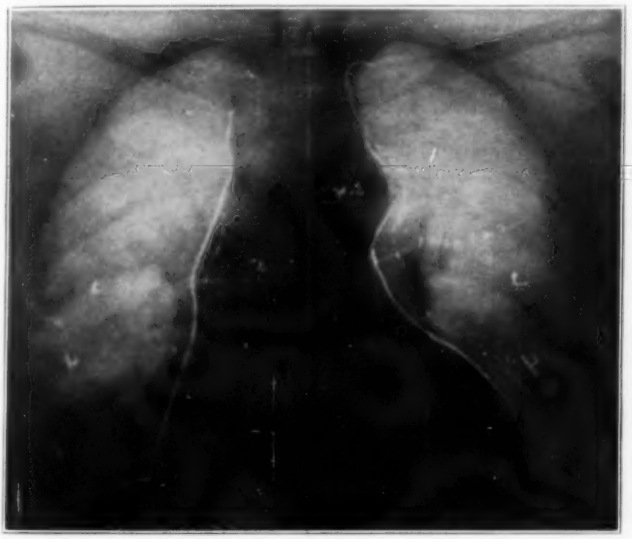

Fig. 2 (C. H., Table 2).—Slight increase in heart size with cessation of tachycardia.

plates upon one another, using two fixed points, such as the junctions of the transverse processes with the tubercle of the first rib. The arch of the aorta and the lateral chest walls also served as checks in superimposing plates. In this manner, heart outlines of any number of films may be drawn on a single one, for purposes of comparison. The dotted line in this figure represents the condition at discharge, at which time the fibrillation and tachycardia had ceased. It will be seen that not only was there no retraction of the borders, but slight movement of the left border outward (0.9 cm.). It is believed by some that a cessation of paroxysmal tachycardia is accompanied at times by

TABLE 2.—*Patients Leaving Hospital with Hearts More or Less Compensated with Heart Outlines Unchanged*

Name	Age	Lesion	Decompensation	Improvement	Dates	Cardio-thoracic Ratio	Percussion Measure			Roentgen-Ray Measurements			Urine, C.c.	Pulse	Remarks
							Right	Left	Total	Right	Left	Total			
C. H.	58	Myocarditis, aortitis, aortic stenosis and insufficiency fibrillation	Pain and palpitation	Yes; fibrillation ceased, pulse slow	1st admis. 7/ 7/22 2d admis. 10/30/22 11/ 6/22 11/28/22	0.64	Discharge			6.5	10	= 16.5	240+	60-80	No change
							7.3	11	= 18.3	6.5	9.5	= 16.0	420	140-152	
							6.5	10.5	= 17.0	7.9	8.5	= 16.4	1,140+	68-80	
							5.4	11.7	= 17.1	6.8	10.1	= 16.9	606	52-64	
A. F.	14	Double mitral	Slight, liver not enlarged, edema absent	Slight	10/14/22 10/26/22	0.64	4	12	= 16	5.2	9.2	= 14.4	510	96-120 (in bed)	No change
							3.3	10.7	= 14	4.5	10.5	= 15.0		84-100 (up)	
M. O.	45	Mitral stenosis and insufficiency, myocarditis	Moderate; cyanosis and edema, precordial pain	Yes; but some distress remained fibrillation ceased	1/24/23 2/ 2/23 2/ 8/23	0.69	4.8	12	= 16.8	5.8	9.8	= 15.6	900	72-80 fibrill.	No change
							5.0	10.5	= 15.5	5.9	10	= 15.9	480	68-84	
							5.5	11.3	= 16.8	4.8	10.6	= 15.4	480	72 reg.	
B. B. 1st admission	30	Double mitral and fibrillation	Present; liver 3 fingers below, no edema	Yes	11/23/22 12/30/22	0.65	3.7	9.5	= 13.2	6.6	11.2	= 17.8	680	96 irreg.	No change
							4.7	11.0	= 15.7	6.2	11.7	= 17.9		80-84 irreg.	
B. W. 4th admission	28	Double mitral	More dyspneic. Less dyspnea, liver still enlarged and tender on discharge	Yes; fibrillation ceased	1/25/23 2/14/23 2/20/23	0.67	5.5	12.5	= 18	7.0	12.3	= 19.3	540	80-100	No change
							6.2	13	= 19.2	6.9	12.4	= 19.3		72 reg.	
							5.3	12.5	= 17.8	7.1	12.0	= 19.1			
E. L. 2d admission	32	Double mitral fibrillation	Yes	Slight	1/27/23 2/26/23	0.74	6	14.5	= 20.5	5.5	13.2	= 18.7	...	.....	No change
							5	13.1	= 18.1	6.4	12.2	= 18.6			
B. T.	45	Double mitral fibrillation	Yes	At discharge first time	4/21/22 6/30/22	0.75	7	12	= 19	7.5	12.0	= 19.5	500	.....	No change
							4.5	12.5	= 17.0	6.9	13.0	= 19.9	1,500		

an increase in heart size due to greater filling during diastole. The pulse rate of the patient mentioned in the foregoing on entrance was: 140 to 152; on discharge: 52 to 64. In another case (M. O., Table 2) in which the slow fibrillation (72 to 80) gave place to sinus rhythm with a pulse rate of 72, there is no change in position of the left border. In three patients belonging to group (*c*) fibrillation ceased during the period of observation. In the first patient (B. G., Table 3), when sinus rhythm was restored there was slight retraction of the left border and of the left auricle and superior vena cava of the right border. In the second (I. B., Table 3), fibrillation began again during the early part of her stay in the hospital. At this time there was a movement outward of all borders. On the second cessation of fibrillation, the borders again clearly retracted. In the third case (B. W., Table 3), there was no change of borders on the cessation of fibrillation. To sum the matter up, there is apparently no fixed rule for change in heart size or shape when fibrillation ceases. All borders may become smaller or remain unchanged. Considering the percussion figures alone in this group, we would have diagnosed a diminution in size of the heart on discharge in every case but two. As a rule, the percussion figures for the transverse diameter were 1 to 2 cm. greater than the roentgen-ray figures. Probably the limit of error in percussing the transverse diameter is 2 cm.

Group (*c*) (Table 3) includes the remaining cases, namely, patients leaving the hospital improved and with heart outlines changed. There were thirteen in this group, including three already considered in other groups on different admissions. There were five cases of myocarditis, seven of mitral lesions and one of aortic insufficiency. Subdividing these again according to the heart divisions which showed a change during compensation, we find seven cases which showed retraction of all borders including the superior vena cava and pulmonary artery; four cases improved with retraction of the right border alone, one case showed retraction of the left border alone (on one admission) and two cases showed retraction of great vessels alone. An illustration of retraction of all borders including the great vessels in a case of myocarditis is given in Figure 3 (M. A. of Table 3). It will be noticed that the diminution involves the following curves: first, the upper right curve extending in this figure to the third interspace, that is, the border of the superior vena cava; second, the lower right curve from the third interspace to the cardiohepatic angle, the curve of the right auricle; third, middle left curve from the third rib to the fifth interspace, that is, the curve of the pulmonary artery; and fourth, the lower left curve or that of the left ventricle. The diminution in diameter of the base of the heart at the level of the third interspace (through the great vessels) is 1.5 cm. The diminution in the usual transverse diameter,

TABLE 3.—*Patients Leaving Hospital Improved with Heart Outlines Changed*

Name	Age	Lesion	Decompensation	Improvement	Dates	Cardiothoracic Ratio	Percussion Measure			Roentgen-Ray Measurements			Urine, C.c.	Pulse	Remarks
							Right	Left	Total	Right	Left	Total			
H. B.	53	Myocarditis, chronic bronchitis	Yes; dyspnea and edema, cough for 20 years	Yes	1/12/22 1/20/22 11/15/22	0.57	6.0 3.0 4.0	10.0 = 16.0 8.0 = 11.0 10.0 = 14.0		6.1 3.5 3.7	11.0 = 17.1 9.5 = 13.0 10.9 = 14.6		240 480	88-104 72-76 84 standing	Retraction both borders, 4.1 cm.
H. S.	65	Myocarditis, fibrillation, electrocardiogram showed left preponderance and fibrillation	Yes	Yes	11/23/22 12/ 6/22 12/18/22	0.56	4.5 5.0 3.5	13.5 = 18.0 15.2 = 20.2 14.0 = 17.5		4.4 4.2 4.5	13.9 = 18.3 12.0 = 16.2 11.8 = 16.3		750	116 fibrill. 60-70 64-88	Retraction left ventricle and superior vena cava
S. C.	50	Myocarditis, chronic interstitial nephritis	Yes	Yes	4/22/22 5/ 7/22 4/22/22 5/17/22	0.78	5.0 3.5	15.0 = 20.0 15.0 = 18.5		8.8 8.3 Diam. 2d 1.5, 9 cm. Diam. 2d 1.5, 6.6 cm.	13.8 = 22.6 12.8 = 21.1		400 1,300	.....	Retraction both borders, especially superior vena cava and pulmonary artery; marked diminution of pulmonary edema; hilum congested and increased sharpness of heart curves; diminution in transverse diameter 1.5 cm., in great vessels 2.4 cm.
M. A.	62	Myocarditis, emphysema and arteriosclerosis	Yes	Yes	1/ 5/23 1/23/23	0.508	4.5 3.3	10.7 = 15.2 9.4 = 12.7		4.6 4.5	10.5 = 15.1 8.4 = 12.9		360 480	84-116 60-84	Marked diminution in transverse diameter, especially pulmonary artery and right auricle
Mrs. J.	44	Myocarditis, fibrillation	Yes	Yes	12/ 4/22 12/16/22 1/ 9/23	0.78	5.8 5.5 5.0	11.5 = 17.3 13.5 = 19.0 12.5 = 17.5		? ? 7.3	12.5 12.0 12.2 = 19.5		550 900	112-126 108 apex 88 apex	Retraction of border of superior vena cava and pulmonary artery; no change in transverse diameter
V. G. 1st stay hosp.	42	Double mitral	Marked edema	Decided	7/29/22 9/ 6/22	0.68	4.0 4.0	arnd. 17.5 = 21.5 str. 13.5= 17.5		5.7 5.5	11 = 16.7 9.7 = 15.2		525 not meas.	96-120 80-92	Retraction of left ventricle
2d stay in hosp.		Same	Not so marked, slight edema, liver 4 fingers below arch	Marked	10/21/22 11/29/22	0.64	4.5 5.4	13.5 = 18.0 11.0 = 16.4		5.4 4.8	12.5 = 17.9 11.0 = 15.8		1,350 —	84-100 —	Retraction of both borders; diminution in diameter of great vessels, second interspace, 3 cm.

H. E.	52	Double mitral fibrillation	Yes	Yes	11/18/22 12/ 6/22	0.77	7.4 6.5	16.7 = 24.1 16.7 = 23.2	10 8.4	14.0 = 24.0 14.4 = 22.8	1,740 1,380	130 apex 72	Marked diminution in size right border especially due to retraction of portion of left auricle projecting beyond right; slight retraction of pulmonary artery
B. W.	28	Double mitral disorder	Dyspnea; pain; liver 4 fingers below; no edema	Yes	2/ 8/22	0.67	7.0	12.5 = 19.5	5.5	12.2 = 17.7	600	152 irreg.	Diminution in size of right border, especially superior vena cava and right auricle
		2d admission	Slight dyspnea; liver 2 fingers below	....	6/ 6/22		6.0	12.5 = 18.5	6.7	12.0 = 18.7	800	76-80 reg.	
		After second discharge	Still dyspneic, working part of the time, does not feel well	....	11/16/22		4.2	12.6 = 16.8	5.6	12.3 = 17.9	...	80 reg.	
		3d admission	Slightly more dyspneic	....	12/25/22		5.5	12.5 = 18.0	5.9	13 = 18.9			
B. G.	27	Double mitral fibrillation	Moderate; liver 4 fingers below, not tender; no edema	Subjective, with quinidin, sinus rhythm	10/24/22 11/ 8/22	0.65	5.3 4.0	10.8 = 16.1 10.7 = 14.7	Trans. diam. 3d space 10.4 6.8 5.9 Trans. diam. 3d space 8.3	9.3 = 16.1 10.3 = 16.2	870	88 60	Retraction of right border due to diminution in size of left auricle and superior vena cava; no change in transverse diameter; diameter in third space diminished 2.1 cm.
I. B.	45	Double mitral fibrillation	Slight	Yes; fibrillation ceased	9/30/22 10/ 3/22 11/24/22	0.62	2.5 3.5 3.0	10.0 = 12.5 10.5 = 14.0 10.2 = 13.2	4.0 4.8 Trans. diam. 2d 7.0 4.2 Trans. diam. 2d 6.5	8.8 = 12.8 8.3 = 13.1 8.0 = 12.2	... 650	76 reg. 72 irreg. norm. and reg.	Retraction of both borders
B. B. 2d stay in hosp.	40	Double mitral fibrillation	Yes	Yes	1/13/23 1/19/23 2/ 5/23	0.73	5.3 5.0 4.5	13.5 = 18.8 11.8 = 16.8 9.5 = 14.0	7.3 7.2 4.9	11.6 = 18.9 10.9 = 18.1 11.2 = 16.1	1,140 ... 900	92-80 irreg. 64 irreg. 72 irreg.	Marked retraction of right border, slight of left; diminution in third space 2.3 cm.
M. K.	22	Double mitral and aortic	Yes; pain marked, liver tender and 3 fingers below	Yes; dyspnea and pain less, liver barely palpable	1/28/23 2/ 2/23 2/12/23	0.74	7.3 5.3 4.5	12.4 = 19.7 13.0 = 18.3 13.5 = 18.0	7.8 7.2 6.1	10.9 = 18.7 10.7 = 17.9 11.4 = 17.5	900 720 1,320	64-84 reg. 72-92 reg. 76-92 reg.	Diminution in size of right auricle and superior vena cava; slight retraction of left auricle and pulmonary artery returning to typical aortic insufficiency outlines
E. L. 1st admission	32	Double mitral fibrillation	Yes	Yes	12/ 8/22 12/20/22 1/13/23	0.73	4.2 5.5 5.5	14.5 = 18.7 13.0 = 18.5 14.6 = 20.1	6.1 6.2 6.0	12.8 = 18.0 13.1 = 19.3 13.3 = 19.3	1,500 400 (diarrhea)	80-96 irreg. 80-84 irreg. 76-88 irreg.	Retraction only of pulmonary artery, 0.4 cm.

that is, through the widest points of the right auricle and left ventricle, is 2.2 cm. To be noted is the relatively large change in the size of the superior vena cava and pulmonary artery.

In Figure 4 (B. B., Table 3) a double mitral lesion with fibrillation is presented. On first admission, there was moderate improvement subjectively but no change in heart outlines (B. B., Table 2). She

Fig. 3 (M. A., Table 3).—Retraction of all borders. The solid line indicates the condition on admission Jan. 5, 1923; the dotted line, on discharge Jan. 23, 1923. Note pulmonary artery and superior vena cava.

returned in three weeks with decompensation, with the transverse diameter 1 cm. greater than on the previous discharge. The improvement during this stay was marked by two stages of retraction: First, at the end of a week there was a retraction of the whole left border, especially marked in the region of the pulmonary artery, and a slight change in the contour of the right border, indicated by a more acute

angle at the junction of the superior vena cava and the right auricle probably due to retraction of a projecting border of the left auricle. Second, after a further stay of two and one-half weeks, another film showed the left border unchanged and the right border markedly diminished, involving this time the superior vena cava and the right auricle. The part played by the right ventricle in such a contraction is not accurately determined by this method. The total diminution in size of great vessels measured in the third interspace is 2.3 cm. The diminution in usual transverse diameter (*ML* and *MR*) was 2.8 cm.

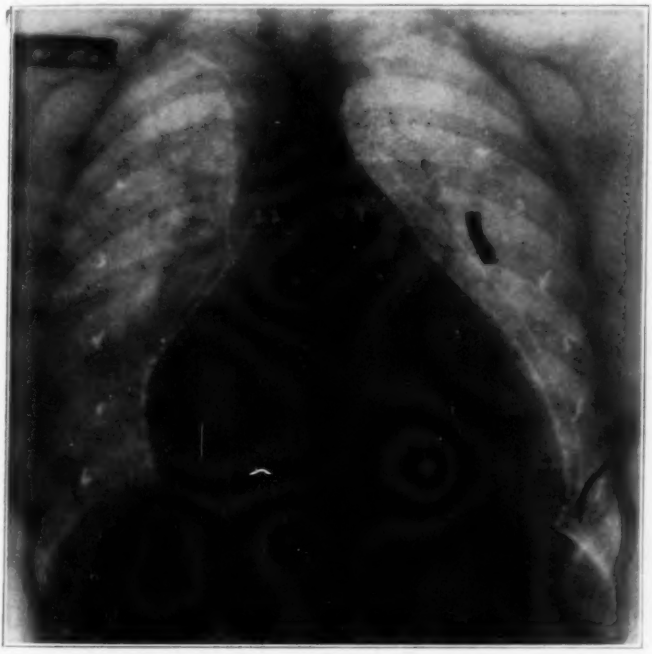

Fig. 4 (B. B., Table 3).—At first there was retraction of left border only; later of right border. The outer solid lines indicate condition on Jan. 13, 1923; the dotted lines on Jan. 19, 1923; and the inner solid lines on Feb. 5, 1923; left border coincides with dotted line.

The marked diminution in size of the great vessels compared with the change in the usual transverse diameter noted in Figure 4 and the preceding one was noticeable also in four other cases in this group. In one (V. G., Table 3) the diameter of the base diminished 3 cm., the transverse diameter, 2.1 cm. In another (S. C., Table 3) the diameter at the base diminished 2.5 cm., the transverse 1.5 cm. In two others, the decrease was either equal to or slightly less than that of the trans-

verse diameter. The average decrease in the diameter of the great vessels in group (*c*) was 1.5 cm.; the average decrease in transverse diameter of the heart in this group was 2 cm. The importance of this point lies in the fact that percussion of the borders of the heart base is quite unreliable (for example, marker in Fig. 4). In contrast with this it will be noted from the figures in Table 3 that the percussion measurements of the transverse diameter of the heart agreed fairly well with the teleoroentgenographic measurements.

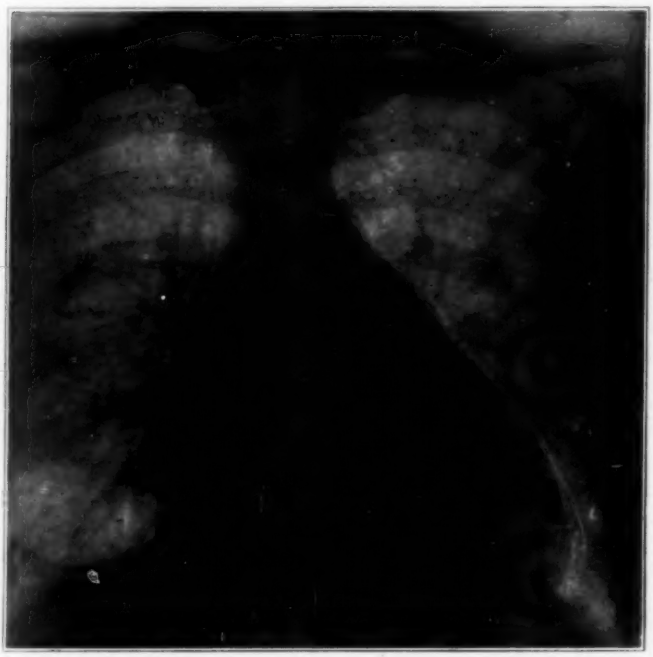

Fig. 5 (B. W., Table 3).—Change in right border only. Inner dotted line shows condition on Nov. 16, 1922. The patient was ambulatory. Outer solid line indicates condition on fourth admission, Jan. 25, 1923. Middle solid line indicates condition on fourth discharge, Feb. 20, 1923.

Figure 5 (B. W., Table 3) is an illustration of retraction of the right border alone. The patient had a double mitral lesion with periods of fibrillation. The plate in the illustration was taken when the patient was out of hospital doing light work. On readmission, again because of decompensation with fibrillation, the whole right border had extended outward, indicated by the outer-most solid line. After a stay of about four weeks, the right border again retracted to the area indicated by

the middle solid line, a distance of about 1 cm. The middle curve on the right side extending from the second to the fourth interspace is possibly due to a projecting left auricle. Periods of improvement, then, were marked by retraction of the right and left auricles and superior vena cava, the left border remaining unchanged, that is, reduction in size of the right and left ventricles was not a factor in producing com-

Fig. 6 (H. E., Table 3).—Change mostly in right border. The innermost dotted line on the right side does not indicate the change in heart size but the junction of an inner dense shadow and an outer lighter one.

pensation. Another point to be mentioned is the clearing up of lung detail in the last plates taken of this patient, as well as the increased sharpness of heart outline, both due to diminished engorgement and edema. In several other cases, the same points were noted. In one (D. F., Table 1) there was no subjective improvement, no change in heart outline, and still a diminution of pulmonary edema.

In Figure 6 (H. E., Table 3) a case of double mitral disorder with fibrillation, the greatest change is in the right border, especially in fourth and fifth interspaces. The most striking feature in the series of plates of this case is the lighter shadow projecting to the right of the innermost dotted line, evidently due to a greatly distended superior vena cava and right and left auricles. Improvement was indicated by retraction of this lighter shadow only, especially in the fourth and fifth interspaces. This is most probably due to retraction of the left

Fig. 7 (V. G., Table 3).—First admission, retraction of left border only.

auricle, which in such cases projects from the posterior heart surface beyond the right auricle, as has been demonstrated by Assmann and Neumann. The darker shadow within the inner dotted line is due to the right ventricle which remained unchanged during compensation. There was a slight change in the pulmonary artery region, part of which may also be due to the left auricle retraction. B. G., Table 3, belongs to this subgroup (retraction of the right border only). Here, too, the most striking feature was a retraction in the third and fourth right

interspaces, also due to the projecting left auricle. A similar change was noted in the discussion of B. B. (Fig. 4). In another patient (M. K., Table 3), who had an aortic insufficiency, the change during compensation was also most marked in the right border, that on the left being limited to a slight retraction in the pulmonary artery region restoring the curve to the aortic insufficiency type.

In Figure 7 (V. G., Table 3) is shown a double mitral disorder in which improvement on the first admission was accompanied by a retrac-

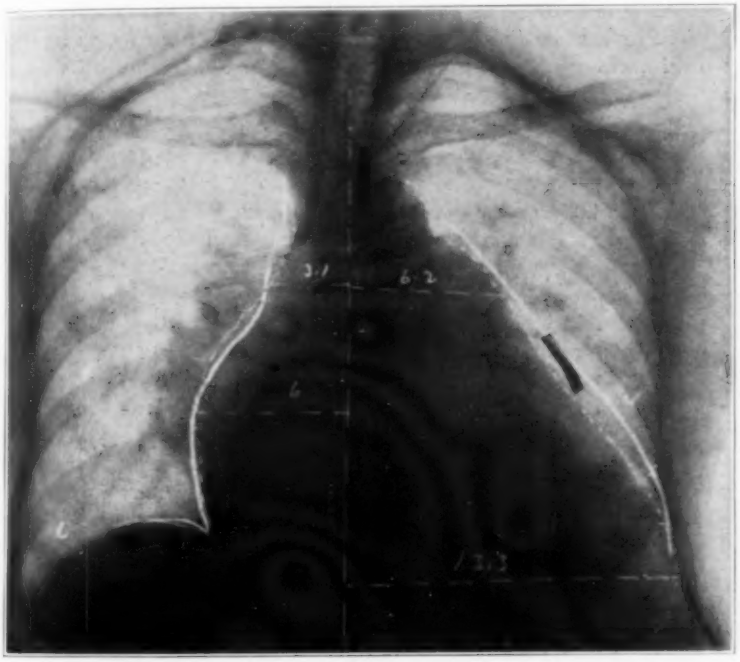

Fig. 8 (E. L., Table 3).—Marked retraction of distended pulmonary artery.

tion of the left border only. This is the only case of the kind in the series. A point of interest in this patient is the fact that though decompensation was not so marked on second admission as on first, the heart was larger. It has, of course, often been pointed out that the size of the heart bears no necessary relation to its functional capacity. Another feature of this case is the fact that on a later admission improvement was accompanied by a retraction of all borders.

Figure 8 is an example of unchanged heart borders except in the area of the great vessels, here limited to the region of the pulmonary

artery in the second and third interspaces. Though less marked at discharge, the projection in this area was still present. Although in only two instances of this series were the changes limited to the great vessels, as a part of right and left border changes, we have previously pointed out their importance.

In summing up groups (*b*) and (*c*) we find that in 35 per cent. of patients recovering compensation, there was no diminution in the diameter of the heart or great vessel. In 35 per cent. more there was diminution in all diameters. In the remaining 30 per cent., there were changes in one border only, most frequently in the right.

The diminution in great vessel diameter varied from 0.4 to 3 cm., that in transverse heart diameter from 0.8 to 4.1 cm.

CONCLUSIONS

1. Cardiac compensation may be restored without any change in any diameter of the heart, with changes only in the great vessels, especially in the superior vena cava and pulmonary artery, with changes in the right or left borders or with changes in all borders. At times the change in the right border is due to the retraction of the projecting left auricle.

2. A total change of 1 cm. in the transverse diameter is within the limits of roentgen-ray error. A change of less than 1 cm. when accompanied by change of shape may have considerable significance.

3. Most striking is the slight change in the left border as compared with the right.

4. The most frequent change is that at the base, namely, the superior vena cava and pulmonary artery. This variation cannot usually be determined by percussion. Therefore variations in size in chronic heart conditions determined by percussion alone are unreliable.

5. In cases in which decompensation occurs more than once, different divisions of the heart may be affected each time, although the clinical pictures presented are identical.

6. In chronic heart disease there may be marked variation in function, with slight or no variation in size.

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OBSERVATIONS ON THE INFLUENCE OF PITUITARY EXTRACT ON THE METABOLISM IN DIABETES INSIPIDUS *

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The chief disturbance associated with diabetes insipidus relates to water metabolism, and in any discussion of the subject the changes induced in normal persons by drinking water copiously must be kept in mind. Voit [1] pointed out that there is a small increase in nitrogen elimination after copious water intake, although Straub [2] found no effect on nitrogen equilibrium of man following the extra ingestion of 2 liters of water. Heilner [3] found increased elimination of nitrogen in fasting dogs after the intake of 2 liters of water each day for two days. Hawk [4] gave more water and less protein to human beings and found that 4,500 c.c. of water each day raised the urine nitrogen from 11.03 to 12.48 gm. on the first day, and to 11.82 gm. on the second day, with a secondary fall to 10.91 gm.

Rosenbloom and Price [5] studied the metabolism of a boy, aged 4 years, suffering from diabetes insipidus. They found a normal amount and partition of urinary nitrogen. Increased protein intake was followed by increased nitrogen output. A low percentage of nitrogen was found in the stool, as compared with the nitrogen intake. They consider that the increased ingestion of water favors the absorption of nitrogen from the gastro-intestinal tract, which Hawk has shown lessens the amount of fecal nitrogen excreted. These authors believe that there is no important change in the state of nutrition or protein metabolism in this disease. The chlorin metabolism was normal, except that an increased sodium chlorid intake resulted in larger quantities of

* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine, October, 1922.

1. Voit, quoted by Lusk, G.: Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Company, 1919, p. 162.

2. Straub, W.: Ueber den Einfluss des Kochsalzes auf die Eiweisszersetzung, Ztschr. f. Biol. **19**:527-549, 1898-1899.

3. Heilner, E.: Ueber die Wirkung der Zufuhr von Wasser auf die Stickstoff und Chloralasscheidung im Harn, Ztschr. f. Biol. **47**:538-561, 1906.

4. Hawk, P. B.: Studies on Drinking Water, Univ. Penn. Med. Bull. **17**:7, 1905. Fowler, C. C., and Hawk, P. B.: Studies on Drinking Water. II. The Metabolic Influence of Copious Water Drinking with Meals, J. Exper. M. **12**:388-410, 1910.

5. Rosenbloom, J., and Price, H. T.: A Metabolism Study of a Case of Diabetes Insipidus, Am. J. Dis. Child. **12**:53-60 (July) 1916.

urine and no change in chlorin concentration in the urine. The metabolism of sulphur, calcium, phosphorus and magnesium was also normal.

Gibson and Martin [6] found a high level of ammonia and of undetermined nitrogen in the urine in a case of diabetes insipidus before the administration of pituitary extract; a considerable nitrogen retention with a lessened elimination and a more normal nitrogen partition after the administration of pituitary extract; and a return to the former condition as the effects of the drug disappeared.

Christie and Stewart [7] found a slightly decreased electrical conductivity of the blood of normal persons after the ingestion of large amounts of water, indicating a more dilute serum in respect to electrolytes, and, on restriction of fluids, a slight increase in the electrical conductivity of serum, and a corresponding decrease in volume relative to corpuscles. In a case of diabetes insipidus, after voluntary restriction of fluid intake or after pituitary extract administration, they found a definite but slight increase in the conductivity of the serum and a corresponding slight decrease in its volume, relative to the corpuscles. In a recent publication [8] these authors report similar studies in two further cases of diabetes insipidus, finding no definite changes in the electrical conductivity of the serum, or its precentage volume before and after water deprivation. Furthermore, there was no change, either one-half hour or five to six hours after resumption of water ingestion, other than a slightly greater percentage of serum in the specimen taken after five to six hours.

Williams [9] found sodium chlorid elimination in diabetes insipidus was on a higher plane after administration of pituitary extract.

Rabinowitch,[10] in the study of a case of diabetes insipidus, found a normal nitrogen balance, but hyperchloremia, and high salt threshold and salt retention. Sodium chlorid stimulated the kidney by lowering the threshold in proportion to the amount of the chlorid given. After pituitary extract had been given, there was increased salt excretion and concentration.

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6. Gibson, R. B., and Martin, F. T.: Administration of a Pituitary Extract and Histamin in a Case of Diabetes Insipidus, Arch. Int. Med. **27**:351-360 (March) 1921.

7. Christie, C. D., and Stewart, G. N.: Study of a Case of Diabetes Insipidus with Special Reference to the Mechanism of the Diuresis and of the Action of Pituitary Extract on it, Arch. Int. Med. **20**:10-23 (July) 1917.

8. Christie, C. D., and Stewart, G. N.: Study of Some Cases of Diabetes Insipidus with Special Reference to the Detection of Changes in the Blood when Water is Taken or Withheld, Arch. Int. Med. **29**:555-566 (May) 1922.

9. Williams, J. R.: Diabetes Insipidus. A Metabolic Study of the Effect of Pituitary Administration, Endocrinology **1**:312-325, 1917.

10. Rabinowitch, I. M.: Metabolic Studies on a Case of Diabetes Insipidus, Arch. Int. Med. **28**:355-366 (Sept.) 1921.

Leschke [11] studied two cases of diabetes insipidus under normal conditions and on restriction of fluids (thirst). His data would indicate a concentration of the blood in the latter condition.

Brunn [12] reports evidence of a hydremia after the administration of pituitary extract to patients with diabetes insipidus and to normal persons. The drug temporarily blocked the kidneys to water secretion. Konschegg and Schuster [13] found dilution of the blood after the administration of pituitary extract.

Priestley [14] investigated the effects in normal persons of drinking water copiously and found no change in the hemoglobin, or the oxygen content of the blood. The electrical conductivity was decreased. By the determination of the total solids and of the plasma chlorids, he demonstrated a slight dilution of the blood during the diuresis following ingestion of 2 liters of water. Administration of pituitary extract delayed the diuresis for from four to six hours; if it had already begun, the drug cut it short at once. The interference with absorption from the gastro-intestinal tract produced by the drug, as claimed by Rees,[15] is slight, and not sufficient to account for the prevention of this diuresis.

In general, it is agreed that increased water intake by normal persons results in a slight increase in the urinary nitrogen elimination, while the fecal nitrogen is diminished because of better absorption. It is likewise agreed that in cases of diabetes insipidus, a slight dilution of the blood serum occurs after the administration of pituitary extract. There is some difference of opinion with regard to the elimination of urinary nitrogen and chlorin in this disease before and after administration of the pituitary extract. However, no striking disturbance in the metabolism of these elements has been noted.

CLINICAL MATERIAL STUDIED AND METHODS UTILIZED

Comprehensive studies [16] were made of the blood and urine of two cases of diabetes insipidus (Cases 1 and 2). The studies in the second

11. Leschke, E.: Beiträge zur klinischen Pathologie des Zwischenhirns. I. Klinische und experimentelle Untersuchungen über Diabetes insipidus, seine Beziehungen und zur Hypophyse und zum Zwischenhirn, Ztschr. f. klin. Med. **87**:201-279, 1919.

12. Brunn, F.: Ueber diureschommende und diuretische Wirkung des Pituitrins, Zentralbl. f. inn. Med. **41**:674-679, 1920.

13. Von Konschegg, A., and Schuster, E.: Ueber die Beeinflussung der Diurese durch Hypophysenextrakte, Deutsch. med. Wchnschr. **2**:1091-1095, 1915.

14. Priestley, J. G.: The Regulation of the Excretion of Water by the Kidneys, J. Physiol. **55**:305-318, 1921.

15. Rees, M. H.: The Influence of Pituitary Extracts on the Absorption of Water from the Small Intestine, Am. J. Physiol. **53**:43-48, 1920.

16. These studies were completed by March, 1921, and preceded the publication of several of the articles mentioned in the references.

case were repeated during the patient's subsequent admission to the hospital. Studies of the blood were made in two other cases (Cases 3 and 4) and in normal persons. An attempt was made to ascertain changes in the metabolism and excretion of water, nitrogen and chlorids during the administration of pituitary extract and variations in the composition and volume of the blood incident to these changes. All of the subjects were under careful control in the hospital. Freedom of water intake was allowed, but the amounts were carefully measured. A constant diet was maintained and some of the articles of food were analyzed for total nitrogen and sodium chlorid. Pituitary extract, when given, was injected sufficiently often to insure continuance of action. Great care was taken in the collection of specimens, and duplicate analyses were made as follows: Total nitrogen of urine, plasma, feces and food, Kjeldahl method; urine chlorids, Volhard method; blood chlorid, Rappleye method; food chlorids by Volhard's method after ashing; urea, creatinin, uric acid in urine and blood, according to the methods of Folin and Wu; urinary ammonia, Malfatti method; urinary acidity, titration with 0.1 normal alkali; total nonprotein nitrogen, Folin's method; blood sugar, Benedict's method; molecular concentrations from depression of the freezing point; relative plasma volume by the hematocrit; and water content of feces by drying to a constant weight.[17]

EFFECTS OF PITUITARY EXTRACT ON METABOLISM OF WATER, NITROGEN AND CHLORID IN TWO CASES OF DIABETES INSIPIDUS

Case 1.—Mr. C. N. N., aged 47 years, came to the Clinic on April 23, 1920. He had had typhoid at the age of 12 and a syphilitic infection at the age of 24. In June, 1914, he had had pain in the legs and a sudden onset of polydipsia, polyuria and weakness. In 1915, he had had transient attacks of diplopia. His weight increased to 220 pounds (99.7 kg.), but this lasted only a few months. For the last five years there had been slight incontinence of urine. Libido and potentio had been progressively and persistently diminishing.

At the time of examination, the patient weighed 175 pounds (79.3 kg.). His pupils reacted slowly to light and to accommodation, and were irregular. Incoordination and Romberg's sign were present. The patellar and Achilles reflexes were absent. There was loss of vibration, position and pressure sense. A diagnosis of syphilis of the central nervous system (parenchymatous) was made.

RESULTS OF OBSERVATIONS IN CASE 1

The water intake for each three-hour period before treatment varied from 720 to 1200 c.c., and under treatment, from 0 to 480 c.c. In the period before treatment the water output in the urine for three hours alone varied from 544 c.c. to 980 c.c. (average of specimen from

17. Water balance, as referred to here, is the difference between water intake and urine output. The water content of the food calculated from the tables of Atwater and Benedict, but not the water of oxidation, is included in the figures for the water intake.

8 p. m., July 7, to 8 a. m., July 8), and in the period of treatment from 130 c.c. to 317 c.c. except for the period between 8 p. m., July 10, and 8 a. m., July 11, when the average three-hour excretion was 655 c.c. At this time the effect of solution of hypophysis (Squibb) was apparently wearing off, since from 8 a. m. to 8 p. m., July 9, the excretion was 862 c.c., and for the same period on July 10, 774 c.c., showing uniform action of the drug.

In the balance of water, nitrogen and chlorids (Table 3), the experiment is satisfactory, as the nitrogen and chlorid intakes were uniform. There was no diarrhea after the administration of the drug,

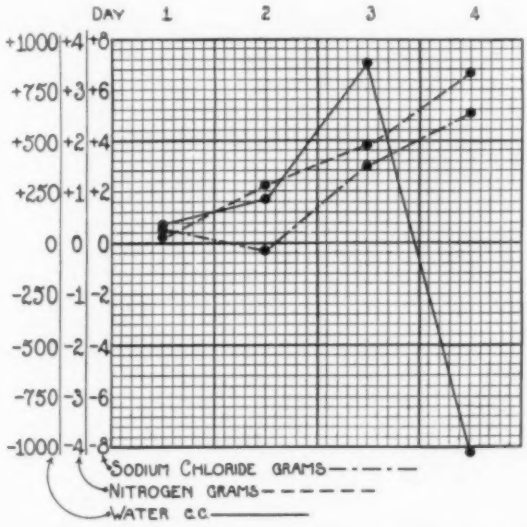

Chart 1 (Case 1).—Balance of water, nitrogen and chlorids during metabolism experiment.

and analysis did not reveal increased elimination of these elements in the feces. The low water balance in the normal period calculated from water intake and output indicated unusually small losses by way of the skin and lungs, provided there was no change in weight. This harmonized well with the clinical observations of dry skin and mouth. The marked increase in the retention of water after the first dose of pituitary extract corresponded to the drop in urinary output. The negative balance on the last day, due to the large excretion of urine from 8 p. m. to 8 a. m., when the effect of the drug had apparently decreased, suggested that the water had been retained. The excretion of nitrogen in the urine was not greatly changed on the first day of treat-

ment, but dropped considerably on the second day. Chlorids in the urine decreased on the first day and were lower on the second day. The nitrogen balance was slightly positive in the period before treatment, with a slight retention on the first day and greater retention on the second day of treatment. The chlorid balance was similar to the nitrogen except that the equilibrium was more nearly established in the period before treatment, and retention in the after period of treatment was more marked. On the last day, the nitrogen and chlorid balances

TABLE 1.—*Water Balance Before and After Administration of Pituitary Extract (Case 1)* *

	Hours of Collection	Water Intake, C.c.			Water Output, C.c.			Balance, C.c.
		In Fluid	In Food	Total	Urine	In Feces	Total	
Before treatment July 7, 1920	8-11	960	475		862			
	11-2	720	475		712			
	2-5	960	.....		823			
	5-8	720	475		721			
	8-8	2,400	.....		3,914	86		
	Total	5,760	1,425	7,185	7,032	86	7,118	+67
July 8, 1920	8-11	1,200	475		544			
	11-2	720	475		755			
	2-5	720	.....		820			
	5-8	960	475		808			
	8-8	1,680	.....		3,480	86		
	Total	5,280	1,425	6,705	6,407	86	6,493	+212
During treatment July 9, 1920	8-11	480	475		248			
	11-2	480	475		317			
	2-5	0	.....		147			
	5-8	480	475		150			
	8-8	0	.....		1,080	40		
	Total	1,440	1,425	2,865	1,942	40	1,982	+883
July 10, 1920	8-11	480	475		130			
	11-2	480	475		198			
	2-5	0	.....		197			
	5-8	480	475		254			
	8-8	480	.....		2,623	40		
	Total	1,920	1,425	3,345	3,397	40	3,437	—1,012

* A specimen of blood was taken at 11 a. m., July 8; at 7:45 a.m., July 9, the patient was given 1 c.c. pituitary extract (pituitrin "O", Parke, Davis & Co.) subcutaneously, and at 11 a. m. the other specimen of blood was taken. At 8 a. m., July 10, 1 c.c. of Squibb's pituitrin was given. (Tables 2, 3 and 10).

were not parallel with the water balance. The variations in urine volume and specific gravity were marked. The excretion of acids and ammonia was slightly lower after the administration of pituitary extract. The percentage of ammonia nitrogen to total nitrogen was also a little lower on the last day.

Referring to the daily totals, it may be noted, especially on the second day of pituitary extract administration, that there was a drop in the excretion of all the materials examined. This accounts for the positive chlorid and nitrogen balance, and indicates a retention of all these substances.

TABLE 2.—*Urinary Partition During a Metabolism Experiment Before and After Administration of Pituitary Extract (Case 1)*

TABLE 2.—*Urinary Partition During a Metabolism Experiment Before and After Administration of Pituitary Extract (Case 1)*

	Time	Volume, C.c.	Specific Gravity	Acidity, C.c. 0.1 Normal Acid	Sodium Chlorid, Gm.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin Nitrogen, Gm.	Uric Acid Nitrogen, Gm.	Urea Nitrogen, Total Nitrogen, per Cent.	Ammonia Nitrogen, Total Nitrogen, per Cent.	Creatinin Nitrogen, Total Nitrogen, per Cent.	Uric Acid Nitrogen, Total Nitrogen, per Cent.
July 7, 1920	8-11	802	1.005	11.0	2.38	1.14	0.93	0.03	0.07	0.02	81.5	2.9	5.8	2.0
	11-2	712	1.006	11.2	1.37	1.15	1.02	0.03	0.06	0.02	88.9	2.8	5.3	1.9
	2-5	823	1.006	26.3	1.60	1.26	0.98	0.04	0.06	0.02	77.8	3.5	4.9	1.6
	5-8	721	1.006	27.7	1.96	1.12	0.91	0.05	0.05	0.01	81.5	4.3	4.9	1.3
	8-8	3,914	1.004	103.3	8.58	4.71	3.69	0.17	0.25	0.07	78.5	2.5	5.4	1.5
	Total	7,032	.....	189.5	15.89	9.38	7.53	0.32	0.49	0.15				
July 8, 1920	8-11	544	1.005	12.9	1.27	0.80	0.59	0.03	0.05	0.01	73.8	3.6	6.8	1.6
	11-2	755	1.005	7.0	1.52	1.05	0.91	0.04	0.06	0.02	86.7	4.1	6.1	1.5
	2-5	820	1.007	85.7	1.35	1.27	1.05	0.06	0.07	0.02	83.1	4.6	5.7	1.3
	5-8	808	1.006	30.0	1.88	1.13	0.93	0.05	0.07	0.01	82.0	4.0	5.9	1.3
	8-8	3,840	1.006	62.3	9.62	4.23	3.47	0.18	0.27	0.06	81.9	4.3	6.3	1.5
	Total	6,767	.....	197.8	15.64	8.48	6.95	0.36	0.52	0.12				
July 9, 1920	8-11	248	1.009	5.2	1.83	0.56	0.46	0.03	0.04	0.01	83.1	5.0	7.9	1.8
	11-2	317	1.013	10.8	2.28	1.19	0.93	0.04	0.07	0.02	78.5	3.4	6.5	1.5
	2-5	147	1.013	11.0	1.02	0.58	0.48	0.02	0.04	0.01	83.0	3.6	6.8	1.2
	5-8	150	1.014	18.4	0.91	0.77	0.65	0.03	0.05	0.01	84.6	4.2	6.0	1.2
	8-8	1,080	1.014	126.9	6.47	5.21	4.36	0.16	0.32	0.07	83.6	3.1	6.1	1.3
	Total	1,942	.....	171.3	12.51	8.31	6.88	0.28	0.52	0.11				
July 10, 1920	8-11	130	1.014	0	0.66	0.75	0.46	0.01	0.04	0.01	61.2	1.5	5.3	1.4
	11-2	193	1.012	20.4	1.02	0.78	0.62	0.01	0.06	0.01	79.0	1.8	7.4	1.7
	2-5	197	1.010	6.7	0.56	0.54	0.45	0.01	0.03	0.01	83.8	2.2	6.5	1.5
	5-8	254	1.010	10.0	0.73	0.63	0.50	0.02	0.04	0.01	79.2	2.8	6.2	1.4
	8-8	2,623	1.006	100.7	8.02	4.55	3.73	0.14	0.28	0.07	82.1	3.1	6.2	1.5
	Total	3,397	.....	137.8	10.99	7.25	5.78	0.19	0.45	0.11				

TABLE 3.—*Balance of Water, Nitrogen and Chlorid During Metabolism Period (Case 1)*

	Intake			Output									Balance			Remarks
				Water, C.c.			Nitrogen, Gm.			Chlorid, Gm.						
	Water, C.c.	Nitrogen, Gm.	Chlorid, Gm.	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Water, C.c.	Nitrogen, Gm.	Chlorid, Gm.	
July 7, 1920	7,185	10.69	16.60	7,032	86	7,118	9.38	1.12	10.50	15.89	0.21	16.10	+67	+0.19	+0.50	Normal
July 8, 1920	6,705	10.52	15.52	6,467	86	6,493	8.49	1.12	9.61	15.64	0.21	15.85	+212	+1.10	—0.33	Normal
July 9, 1920	2,865	10.76	15.52	1,942	40	1,982	8.31	0.49	8.80	12.51	0.07	12.58	+883	+1.95	+2.94	Pituitrin
July 10, 1920	2,345	11.12	15.77	3,397	40	3,437	7.24	0.49	7.74	10.99	0.07	11.56	—1,012	+3.38	+4.71	Pituitrin

Case 2[18].—Mr. C. H. H., aged 39 years, came to the Clinic on Sept. 10, 1920. He gave a history of having had diphtheria and scarlet fever at the age of 6 years; typhoid fever at 7; syphilitic infection with orchitis at 26, and an indefinite illness of gradual onset characterized by weakness, dark yellowish complexion, poor appetite and sleepiness at 32. A physician diagnosed syphilis and advised intensive treatment. Three months later the patient had a sudden onset of thirst and polyuria; he drank from 11 to 14 liters of water daily. About this time he commenced to notice decrease in libido and potentio which progressed to complete loss during the last two years. With the onset of polyuria, he also noticed loss of facial and axillary hair.

At the time of examination, the patient weighed 172 pounds (78 kg.). The skin was dry, lifeless and sallow. The testicles were small and atrophic.

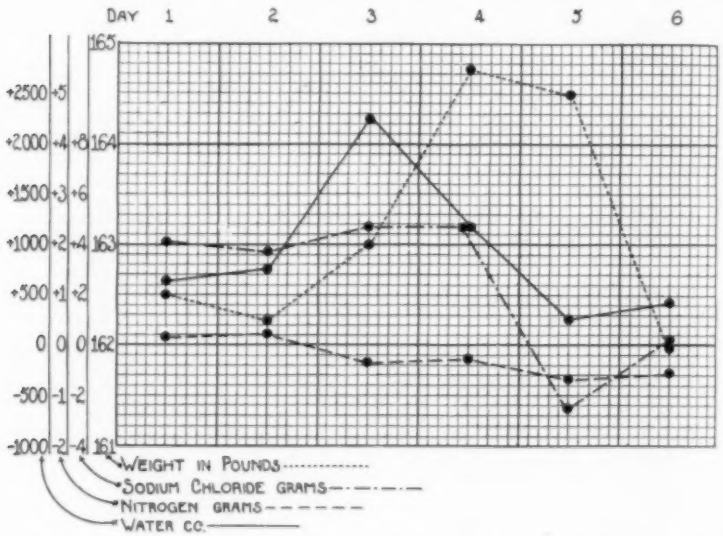

Fig. 2 (Case 2).—Weight and balance of water, nitrogen and chlorids during first metabolism experiment.

The basal metabolism varied from —31 to —15. The spinal fluid revealed a positive Nonnne reaction and 12 lymphocytes. Other laboratory tests were uniformly negative.

RESULTS OF OBSERVATIONS IN CASE 2

In Table 4 the water intake alone for each three hourly period is shown to vary from 200 to 800 c.c. before treatment, from 0 to 398 c.c. (omitting the one period from 11 to 2 on September 3, when 1,000 c.c. were taken) during treatment, and from 0 to 600 c.c. during the period after treatment. The urine output alone varied from 185 to 695 c.c.

18. McNeal, M.D.: The Male Sexual Gland in the Prevention of Creatinuria, Am. J. M. Sc. **164**:222-227, 1922.

in the first period, from 101 to 420 c.c. during treatment, and from 165 to 941 c.c. in the final period. The urine output in the last two days gradually increased in each three-hour period as the effect of the pituitary extract was wearing off, until during the last twelve hours,

TABLE 4.—*Water Balance in the First Metabolism Experiment (Case 2)* *

	Time of Collection	Fluid Intake, C.c.			Fluid Output, Urine, C.c.	Balance, C.c.
		Water	Food	Total		
Before Treatment: Sept. 1, 1920.....	8-11	800	529		287	
	11-2	400	529		396	
	2-5	200	...		700	
	5-8	600	531		557	
	8-8	1,600	...		2,584	
	Total	3,600	1,589	5,189	4,525	+664
Sept. 2, 1920.....	8-11	800	530		705	
	11-2	800	530		750	
	2-5	350	...		185	
	5-8	400	530		560	
	8-8	1,800	...		2,780	
	Total	4,150	1,590	5,740	4,980	+760
During Treatment: Sept. 3, 1920.....	8-11	200	531		135	
	11-2	1,000	531		115	
	2-5	0	...		125	
	5-8	200	531		120	
	8-8	200	...		420	
	Total	1,600	1,593	3,193	915	+2,278
Sept. 4, 1920.....	8-11	200	526		230	
	11-2	200	526		210	
	2-5	200	...		240	
	5-8	200	528		115	
	8-8	0	...		405	
	Total	800	1,580	2,380	1,200	+1,180
After Treatment: Sept. 5, 1920.....	8-11	200	510		165	
	11-2	200	510		175	
	2-5	0	...		195	
	5-8	400	512		405	
	8-8	2,400	...		3,505	
	Total	3,200	1,532	4,732	4,445	+287
Sept. 6, 1920.....	8-11	400	510		660	
	11-2	1,400	510		485	
	2-5	800	...		425	
	5-8	200	512		625	
	8-8	2,050	...		3,765	
	Total	4,850	1,532	6,382	5,960	+422

* In the first experiment, blood was taken before breakfast at 8:30 a. m., September 3 and 4. September 3, at 7:30 a. m., 1 c.c. of pituitary extract (Parke, Davis & Co. pituitrin "S") was given, and blood was withdrawn at 8:40 a. m. The pituitrin was repeated at 8:15 p. m. September 4, at 8:45 a. m., the next specimen was taken. The pituitrin was repeated at 5 p. m. September 5 blood was taken before breakfast, at 8:45 a. m., and September 6 at 8:30 a. m. Symptoms of thirst began about 8 p. m., September 6 (Tables 5, 6 and 11).

when the excretion was higher than at any time during the period before treatment.

The positive balance of water in the normal period was considerably higher than in Case 1 and approximates the amount excreted daily through the lungs and the skin by a normal person. The marked

TABLE 5.—*Urinary Partition on the First Metabolism Experiment (Case 2)*

	Time	Volume, C.c.	Specific Gravity	Acidity, C.c. 0.1 Normal Acid	Sodium Chlorid, Gm.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin Nitrogen, Gm.	Uric Acid Nitrogen, Gm.	Urea Nitrogen, Total Nitrogen, per Cent.	Ammonia Nitrogen, Total Nitrogen, per Cent.	Creatinin Nitrogen, Total Nitrogen, per Cent.	Uric Acid Nitrogen, Total Nitrogen, per Cent.
Sept. 1, 1920	8-11	287	1.004	22.6	0.61	0.68	0.38	0.03	0.05	0.01	56.2	4.4	7.1	1.2
	11-2	390	1.008	38.8	0.58	0.97	0.46	0.05	0.05	0.01	47.2	5.6	5.4	1.0
	2-5	700	1.006	71.6	0.93	1.19	1.03	0.04	0.06	0.01	86.3	3.3	4.6	1.1
	5-8	557	1.006	66.5	0.86	1.16	1.08	0.04	0.05	0.01	92.9	3.9	4.5	1.0
	8-8	2,585	1.010	198.5	2.73	4.24	3.60	0.15	0.11	0.05	85.4	3.4	2.7	1.1
	Total	4,525	.....	398.0	5.70	8.24	6.55	0.31	0.32	0.09				
Sept. 2, 1920	8-11	705	1.005	33.1	0.99	0.96	....	0.02	0.06	0.01	....	2.6	6.7	1.3
	11-2	730	1.007	35.9	1.25	0.95	....	0.03	0.06	0.01	....	3.0	6.2	1.4
	2-5	185	1.019	32.5	0.43	0.76	....	0.01	0.05	0.01	....	0.7	7.1	0.3
	5-8	580	1.006	65.5	0.66	1.05	....	0.05	0.07	0.01	....	4.4	6.2	0.9
	8-8	2,780	1.009	176.5	3.43	4.30	....	0.16	0.27	0.01	....	3.7	6.3	1.7
	Total	4,980	.....	343.5	6.76	8.02	....	0.27	0.51	0.05				
Sept. 3, 1920	8-11	135	1.022	18.0	0.61	0.84	0.64	0.01	0.06	0.01	76.2	1.8	7.4	1.4
	11-2	115	1.029	.....	0.66	0.95	0.56	0.27	0.06	0.01	59.4	26.7	6.4	1.1
	2-5	125	1.030	47.8	0.82	1.04	0.94	0.04	0.06	0.01	90.5	4.2	5.6	0.7
	5-8	120	1.022	63.3	0.48	1.09	0.80	0.04	0.06	0.01	73.0	3.7	5.7	0.9
	8-8	420	1.020	139.0	1.70	4.21	3.15	0.10	0.25	0.03	74.8	2.4	5.9	0.8
	Total	915	.....	268.1	4.27	8.13	5.49	0.46	0.49	0.97				
Sept. 4, 1920	8-11	230	1.023	17.2	0.96	1.31	1.17	0.02	0.07	0.02	89.3	1.5	5.6	1.6
	11-2	210	1.020	54.9	0.74	1.14	1.02	0.04	0.07	0.02	88.9	3.8	5.7	1.3
	2-5	240	1.022	89.5	0.76	1.09	0.90	0.04	0.06	0.01	82.0	3.7	5.2	1.1
	5-8	115	1.037	65.5	0.61	0.89	0.83	0.03	0.06	0.02	93.0	3.7	6.8	1.7
	8-8	405	1.019	128.5	2.54	3.77	3.18	0.07	0.27	0.06	84.3	1.9	7.2	1.5
	Total	1,200	.....	355.7	5.61	8.20	7.10	0.20	0.53	1.13				
Sept. 5, 1920	8-11	165	1.024	14.9	1.11	1.29	1.13	0.03	0.08	0.02	87.7	2.0	6.1	1.6
	11-2	175	1.027	27.0	1.02	1.37	1.01	0.03	0.06	0.02	73.7	2.1	4.5	1.1
	2-5	105	1.021	49.8	0.97	1.14	1.00	0.06	0.06	0.01	87.0	5.8	5.6	0.9
	5-8	405	1.011	69.0	1.09	1.20	1.09	0.06	0.06	0.01	90.3	4.7	5.3	1.1
	8-8	3,505	1.006	157.0	7.67	4.26	3.77	0.14	0.23	0.06	88.6	3.2	5.5	1.4
	Total	4,445	.....	317.7	11.86	9.26	8.00	0.32	0.49	0.12				
Sept. 6, 1920	8-11	660	1.004	30.9	1.22	0.96	0.73	0.03	0.06	0.01	75.8	3.6	6.5	1.4
	11-2	485	1.007	46.6	0.86	0.99	0.79	0.05	0.06	0.01	79.9	5.5	5.8	1.1
	2-5	425	1.009	56.2	0.74	0.98	0.82	0.06	0.06	0.01	84.0	5.8	5.9	1.4
	5-8	625	1.007	68.0	0.84	1.05	0.80	0.05	0.05	0.01	76.5	4.8	4.6	0.9
	8-8	3,765	1.004	217.0	5.77	4.05	3.25	0.11	0.25	0.07	93.3	2.7	6.1	1.7
	Total	5,960	.....	418.7	9.43	8.03	6.39	0.30	0.48	0.11				

TABLE 6.—*Balance of Water, Nitrogen, and Chlorid in the First Metabolism Experiment (Case 2)*

	Intake			Output			Balance			Weight, Pounds	Remarks
	Water, C.c.	Nitrogen, Gm.	Chlorid, Gm.	Water, C.c.	Nitrogen, Gm.	Chlorid, Gm.	Water, C.c.	Nitrogen, Gm.	Chlorid, Gm.		
Sept. 1, 1920	5,189	8.42	9.80	4,525	8.27	5.70	+664	+0.15	+4.10	162.5	Normal
Sept. 2, 1920	5,740	8.22	10.52	4,980	8.02	6.76	+760	+0.20	+3.76	162.25	Normal
Sept. 3, 1920	3,193	7.78	8.98	915	8.14	4.27	+2,278	−0.36	+4.71	163.0	Pituitrin
Sept. 4, 1920	2,380	7.92	10.35	1,200	8.20	5.61	+1.180	−0.28	+4.74	164.75	Pituitrin
Sept. 5, 1920	4,732	8.61	9.36	4,445	9.27	11.86	+287	−0.66	−2.50	164.5	Normal
Sept. 6, 1920	6,382	7.57	9.55	5,960	8.02	9.43	+422	−0.45	+0.12	162.0	Normal

increase in retention of water after the first dose of pituitary extract corresponded to the marked drop in urine output and confirmed the observation made in Case 1. The simultaneous increase in weight (Table 6) in this case, as well as the increased excretion in the final period, indicated a retention of the water in the blood or tissues. The excretion of nitrogen in urine showed no change under administration of pituitary extract, but increased in the first day of the period after treatment. A distinct drop in the chlorids in the urine was noted, under the effects of the drug, with an increased excretion in the period after treatment. The nitrogen balance throughout was negative and showed no appreciable change as in Case 1. The chlorid balance showed a slight retention in the period of treatment and a negative balance in the period after treatment. In this final period, the chlorid balance ran parallel to the water. In the urine, the marked variations in volume and specific gravity were again noted. The excretion of acid and ammonia did not definitely change, and no other characteristic variation in the total or percentage of excretion of the other elements in the urine was noted.[19]

During a second observation, the urine was collected as usual, but examination was made of the twenty-four hour specimen only. The water intake was determined for each twenty-four period.

In the period before treatment the urinary output in three hourly periods varied from 375 to 1140 c.c.; in the period of treatment from 70 (average of specimen from 8 p. m., February 27, to 8 a. m., February 28) to 560 c.c., and in the period after treatment, from 175 to 990 c.c.

Equilibrium was fairly well established in the balance of water, nitrogen and chlorid, by the second day of the period before treatment. The positive water balance did not change appreciably during the period of treatment, but the gain in weight in this period and the large negative water balance and drop in weight in the period after treatment were significant. No definite conclusions could be drawn from the balance of nitrogen and chlorids.

The marked variations in urine volume, specific gravity and molecular concentration, were again seen. No definite variations occurred in the total or percentage excretions of the other elements determined.

EFFECTS OF PITUITARY EXTRACT ON COMPOSITION AND VOLUME OF BLOOD IN FOUR CASES OF DIABETES INSIPIDUS

In Case 1, a decrease in the level sodium chlorid, urea and sugar in the blood was noted after pituitary extract had been administered. There was a

19. The collection of feces in this case was unsatisfactory and the results are omitted.

relative decrease in the amount of plasma. The molecular concentration remained practically unchanged. There was slight increase in uric acid and creatinin.

In Case 2, practically no change in relative plasma volume occurred during the first observation. Molecular concentration was increased on the first day of treatment, but dropped on the second day, was still lower on the first day following cessation of treatment, but rose to its highest level on the succeeding day. The total amount of nitrogen and sodium chlorid decreased during the period of treatment and increased again in the period after treatment. No distinct change was seen in the other elements.

TABLE 7.—*Blood Analysis Before and During Administration of Pituitary Extract (Case 1)*

July, 1920	Hematocrit Plasma, per Cent.		Plasma, Mg. for Each 100 C.c.		Whole Blood, Mg. for Each 100 C.c.				Remarks
			Total Nitrogen	Sodium Chlorid	Urea Nitrogen	Uric Acid	Creatinin	Sugar	
8	62	0.528	..	600	11	5.6	1.2	133	Normal
9	57	0.530	..	573	5	6.6	1.5	93	Pitultrin

TABLE 8.—*Blood Analysis (Case 2), First Observation*

September, 1920	Hematocrit Plasma, per Cent.		Plasma for Each 100 C.c.		Whole Blood, Mg. for Each 100 C.c.					Remarks
			Total Nitrogen, Gm.	Sodium Chlorid, Mg.	Non-protein Nitrogen	Urea Nitrogen	Sugar	Uric Acid	Creatinin	
1	67	0.515	1.171	648	29.8	14.9	128	2.7	1.9	Normal
2	70	0.530	1.142	653	26.5	14.9	108	...	...	Normal
3	69	0.542	1.082	640	26.6	16.2	144	...	...	Pitultrin
4	72	0.551	1.000	625	24.8	14.8	108	...	...	Pitultrin
5	71	0.522	1.099	633	28.1	14.8	108	...	...	Normal
6	69	0.546	1.129	648	27.0	13.3	112	...	...	Normal

Second Observation

1921	Hematocrit Plasma, per Cent.		Plasma for Each 100 C.c.			Whole Blood, Mg. for Each 100 C.c.					Remarks
			Carbon Dioxid, Volume, per Cent.	Total Nitrogen, Gm.	Sodium Chlorid, Mg.	Non-protein Nitrogen	Urea Nitrogen	Sugar	Uric Acid	Creatinin	
Feb. 25	60	0.548	..	1.260	570	28.3	12.5	58	2.3	1.4	Normal
26	60	0.528	58	1.287	...	31.9	17.6	78	2.1	1.7	Normal
27	61	0.530	66	.....	580	28.6	13.2	71	2.4	1.5	Pitultrin
28	60	0.491	66	1.182	500	28.3	15.0	112	2.2	1.5	Pitultrin
Mar. 1	68	0.520	68	1.070	580	32.0	16.7	....	1.9	1.5	Normal
2	68	0.537	68	1.120	595	29.6	15.7	....	2.3	1.5	Normal

During the second period of observation of this case, there was a rather marked increase in the relative plasma volume and decrease in the molecular concentration, with a slight decrease in the total nitrogen of the plasma on the second day of treatment. These changes were preceded on the previous day by a rise in the carbon dioxid combining power of the plasma. In the period after treatment, the molecular concentration returned to its previous level, but the relative plasma volume and carbon dioxid combining power remained elevated. The other elements showed no noteworthy changes.

CASE 3.—A nervous, poorly developed woman, aged 37 years, came to the Clinic on Feb. 24, 1921. She had had typhoid fever at 17, and intense thirst,

polyuria and weakness, headaches, pain in neck, and nervousness began suddenly in March, 1920.

She was somewhat anemic, but the physical examination was essentially negative. Her husband had syphilis with definite evidence of involvement of the central nervous system. In view of this, a lumbar puncture was made, revealing a positive Nonne reaction and 13 lymphocytes for each cubic centimeter. Wassermann reactions and the neurologic examination were negative.

TABLE 9.—*Blood Analysis (Case 3)* *

July, 1920	Hematocrit Plasma, per Cent.		Plasma for Each 100 C.c.		Whole Blood, Mg. for Each 100 C.c.			Remarks
			Total Nitrogen, Gm.	Sodium Chlorid, Mg.	Urea Nitrogen	Uric Acid	Creatinin	
15	61	0.522	1.058	629	5.0	2.4	1.3	Normal
16	55	0.549	1.163	640	5.8	2.4	1.3	Normal
17	67	0.549	0.940	607	6.6	2.4	1.3	Pituitrin
18	67	0.513	0.970	597	6.1	2.3	1.3	Pituitrin

* Blood was taken before breakfast at 8:30 a. m. on July 15 and 16 and at 8:15 a. m. on July 17 and 18. Pituitary extract (Parke, Davis & Co., pituitrin "0") was given in 1 c.c. doses at 6 a. m. and 8 p. m. on July 17 and at 6 a. m. on July 18.

TABLE 10.—*Blood Analysis (Case 4)* *

August, 1920	Hematocrit Plasma, per Cent.		Plasma for Each 100 C.c.		Whole Blood, Mg. for Each 100 C.c.			Remarks
			Total Nitrogen, Gm.	Sodium Chlorid, Mg	Non-protein Nitrogen	Urea Nitrogen	Sugar	
3	66	0.544	0.980	588	28	...	123	Normal
4	65	0.530	0.927	580	23	5.0	114	Normal
5	65	0.501	0.905	565	27	6.3	114	Pituitrin
6	66	0.514	1.022	560	28	5.7	114	Pituitrin
7	61	0.512	0.964	576	28	6.5	...	Pituitrin

* Blood was taken before breakfast at 8:30 a. m. on every day of the experiment, August 3 to 7 inclusive. Pituitary extract (Parke, Davis & Co., pituitrin "0") was given in 1 c.c. doses at 6 a. m. August 5, 6 and 7.

TABLE 11.—*Summary of Blood Changes in Four Cases of Diabetes Insipidus During Treatment with Pituitary Extract*

Case	Relative Plasma Volume by Hematocrit	Molecular Concentration	Total Nitrogen	Sodium Chlorid
Case 1				
1.	Decrease	No change	.....	Decrease
2.	Increase	No change	Decrease	Decrease
Case 2				
1.	No change	Decrease	Decrease	Decrease
2.	Increase	Decrease	Decrease	No change
Case 3.	Increase	Decrease	Decrease	Decrease
Case 4.	No change	Decrease	No change	Decrease

The changes in the blood in this case after the administration of pituitary extract were the most distinct of any studied. The relative plasma volume was increased, and molecular concentration decreased, both indicating a dilution. The plasma content of total nitrogen and sodium chlorid was decreased after the administration of pituitary extract. No noteworthy changes in the other elements occurred.

CASE 4.—A woman, aged 28 years, came to the Clinic on July 5, 1920. She had had frequent attacks of tonsillitis and influenza in 1918 and 1919.

For two years, thirst, polyuria and weakness had gradually developed. She gave a long psychoneurotic-like history that suggested a diagnosis of migraine and petit mal. The urine output and thirst had been excessive for six weeks.

At the time of examination the patient weighed 104 pounds (47.17 kg.). Examination of the heart revealed chronic mitral endocarditis (stenosis and regurgitation); otherwise physical and laboratory examinations were negative.

There was no change in the relative plasma volume or total nitrogen content after administration of pituitary extract. However, there was a marked decrease in the molecular concentration and in sodium chlorid content. The other elements examined remained unchanged.

COMMENT

In viewing these results as a group, it may be noted that all the elements of the blood in these cases are within normal limits, both before and after the administration of pituitary extract.

Table 11 shows that the molecular concentration, total nitrogen and sodium chlorid are usually decreased, and that relative plasma volume usually shows an increase after administration of pituitary extract. These changes seem to indicate a dilution of the blood when the excessive elimination of fluid by the kidneys is checked by the administration of pituitary extract, and contrasts with the absence of such changes in normal persons under the influence of pituitary extract. However, the changes are neither constant nor marked, and too much importance should not be attached to them.

EFFECT OF DRINKING WATER AFTER ADMINISTRATION OF PITUITARY EXTRACT

In Case 1, pituitary extract was administered, and the patient was urged to drink water in the amounts to which he had previously become accustomed. In a few hours he began to complain of headache, dizziness, nausea, malaise and weakness. Perspiration was free. There was evidence of edema at the ankles and in the loose tissues around the eyes. The water intake was at once discontinued, and the edema and symptoms gradually disappeared. The patient later repeated the experiment, but did not drink as much as before. In seven to eight hours, there was a recurrence of the symptoms, but without edema. The blood examination before the experiment began and after the development of symptoms (Table 12) showed a marked increase in relative plasma volume, but no accompanying change in the molecular concentration, total nitrogen, sodium chlorid or urea content of the blood.

In view of this water intoxication, the routine water test of renal function was given in Case 2. At 8 a. m., the patient drank 2,000 c.c. of water within thirty minutes on a fasting stomach. Urine was collected and measured, and the specific gravity determined every half hour for four hours (Table 13). No pituitary extract was given before or during this test. After the ingestion of the water, the

patient noted chilliness and abdominal distress. After from three-fourths of an hour to one hour, he suffered general distress. Then his skin became moist, and he perspired freely. He said, "This is the first real sweat I have had for a long time." Later he became nervous and depressed, and lost "pep." He exhibited no tremor objectively, but experienced a shaking sensation in his limbs. A slight headache developed, his mouth became moist, and he lost thirst throughout the day. During the four hours following the intake of the water, the urine output amounted to only one-half the intake. This suggests, in comparison with normal reactions, an impairment of renal function.

TABLE 12.—*Blood During Intoxication with Water After Administration of Pituitrin (Case 1)* *

July, 1920	Hematocrit Plasma, per Cent.	O	Plasma for Each 100 C.c.		Urea Nitrogen in Whole Blood, Mg. for Each 100 C.c.	Remarks
			Total Nitrogen, Gm.	Sodium Chlorid, Mg.		
19	58	0.527	1.006	555	14	Before pituitrin
20	71	0.528	1.000	551	14	During symptoms after pituitrin

* Blood was taken at 11 a. m. on July 19. At 11 a. m., July 20, 1 c.c. pituitary extract (Parke, Davis & Co., pituitrin "0") was given and the patient ingested 3,120 c.c. of water up to 8 p. m. At 10 p. m. the second specimen of blood was taken.

TABLE 13.—*Result of Routine Water Test of Renal Function (Case 2)*

Time	Volume, C.c.	Specific Gravity
8:30 to 9:00	400	1.005
9:00 to 9:30	320	1.004
9:30 to 10:00	100	1.004
10:00 to 10:30	0	
10:30 to 11.00	200	1.004
11:00 to 11:30	0	
11:30 to 12:00	65	1.007
12:00 m. to 8:00 a.m.	3,500	1.006
Total	4,495	

DISCUSSION

The study of the urine and metabolism of two patients with diabetes insipidus disclosed a marked decrease in volume, with a corresponding increase in the specific gravity and molecular concentration (one patient) of the urine after the administration of pituitary extract. With this decrease in volume, there was a disappearance of the distressing clinical symptom of thirst. The weight during two experiments on the same patient was definitely increased, while the normally slightly positive water balance increased markedly. The urine in the period after treatment was increased above that of the period before treatment, indicating retention and confirming the patient's statement that there was always a temporarily increased amount of urine after

the effect of pituitary extract had worn off. In no instance was there diarrhea after the administration of the drug, and analysis of feces in one case failed to reveal increased elimination of water by bowel.

Great care must be exercised in interpreting changes in the balance calculated from the excretion of nitrogen, chlorids and other elements in the urine. However, there is some evidence of a decreased total excretion of nitrogen, chlorids, acids and ammonia with increasing elimination of these substances again as the effects of the drug disappear. These changes are of minor importance and may readily be due to the outstanding variations in water exchange.

In studying the blood it was found that there was a slight relative increase of plasma volume, and a relative decrease in total nitrogen molecular concentration and sodium chlorid of the plasma after the administration of pituitary extract. These were not constant or marked. However, they suggest a dilution of the blood which may also explain the phenomena of decreased excretion of nitrogen and chlorids in urine.

Changes in the water content of the tissues [20] must not be overlooked, for in the one case in which toxic signs developed from overingestion of water after administration of pituitary extract, definite edema was present. Determinations of blood volume [21] have not given constant results. Blood dilution constitutes an adequate explanation of the relief from the thirst, although a more complicated mechanism than simple dilution is undoubtedly involved. Again, dilution of the blood is one of the most effective methods of increasing urinary secretion in a normal person, but this increase does not occur when pituitary extract has been administered to patients with diabetes insipidus. At least, it is not constant, and some other explanation must be sought. The increase in weight of the patients noted during the experiments, the decrease after, and the changes in water balance prove the retention of water. The occurrence of edema in the toxic patients, and the minor changes in the blood indicate involvement of the body tissues. This may mean a raised renal threshold for water, as well as a change in the relative ease with which water passes from the blood to the tissues as compared with the ease with which it passes from the blood through the kidney. In other words, it is not known whether pituitary extract affects the renal tissue primarily, the water threshold being raised and the retained water distributed according to present known laws, or whether all the body tissues are affected by this drug in a more or less similar manner.

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20. Rowntree, L. G.: The Water Balance of the Body, Physiol. Rev. **2**:116-169, 1922.

21. Weir, J. F.; Larson, E. E., and Rowntree, L. G.: Studies in Diabetes Insipidus, Water Balance, and Water Intoxication. Study I., Arch. Int. Med. **29**:306-330 (May) 1922.

CONCLUSIONS

1. Observations following the administration of pituitary extract to patients with diabetes insipidus confirm the previously recorded findings of a marked decrease in urinary output with corresponding increase in specific gravity and molecular concentration coincident with a temporary disappearance of the distressing clinical symptoms.

2. The simultaneous increase in weight and increase of positive water balance and the increased elimination after the effects of the drug have worn off indicate a retention of water in the blood or tissues.

3. Changes in the excretion of nitrogen, chlorids, acids and ammonia may be due to direct action of the pituitary extract on the kidney or may be secondary to the changes in water excretion.

4. The retention of water in the blood and tissues overshadows any possible retention of nitrogen and chlorin.

5. The blood of these patients presents slight and somewhat inconstant evidences of dilution. The occurrence of edema in one case subsequent to forcing water proves that some, at least, of the retained fluid is distributed to the tissues of the body.

6. Dilution of the blood and an increased tissue content of water produced an increased flow of saliva with the cessation of thirst.

7. The dilution of the blood does not appear sufficient to stimulate the kidneys of patients with diabetes insipidus who have received pituitary extract. However, this dilution is neither marked nor constant, and some change in the renal permeability is undoubtedly induced. The extent to which the tissues are affected is as yet unknown.

8. Forcing water to patients with diabetes insipidus subsequent to administration of pituitary extract leads to the development of toxic manifestations.

9. In diabetes insipidus, pituitary extract raises the secretion threshold of the kidney for many substances, but especially for water. It is not yet clear to what extent it affects the relative ease with which water leaves the vascular system to enter the tissues or to be excreted by the kidney.

GASTROSCOPY IN THIRTY CASES OF GASTRIC NEOPLASM *

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Among all the known pathologico-anatomic forms of gastric tumor, carcinoma alone has been susceptible of diagnosis until the present time. In rare cases a tumor recognized by roentgen-ray examination has proved at operation to be a benign polyp. Still rarer has been the diagnosis of sarcoma from vomited tumor fragments.

Only gastroscopy renders it possible to recognize the different forms of tumor. Through it we shall probably be forced to revise our ideas regarding the symptomatology of new growths. Much investigation is still necessary to reach determinate results.

My observations were made in 400 gastroscopic examinations performed in the Munich-Schwabing hospital. They were made with a gastroscope of my own modification. Examination with this instrument if expertly used is almost without discomfort to the patient. The technic is not easy, and much practice is necessary to apply it safely and painlessly, but the diagnostic results are so excellent that the investigator with some knowledge of endoscopy will not be deterred by this difficulty. In contradistinction to round ulcer, which, if situated at the pylorus, is difficult of examination, all neoplasms of the stomach offer a fruitful field of observation.

BENIGN TUMORS

Only such tumors as are situated on the inner aspect of the stomach can be recognized by the gastroscope. These include myomas, fibromyomas, mucous polyps (solitary or multiple) and papillomas. Lymphangiomas and cavernous angiomas occur but are rare.

A. Fibromyoma.—Fibromyomas are usually small and situated near the cardia. I have diagnosed two cases with the gastroscope.

CASE 1.—T. S., a clerk, aged 60, had lost weight for a year on account of undernourishment. He had pain in the stomach after meals. He had lost his appetite. He did not vomit. There were no objective signs. His tongue was coated. He had pulmonary tuberculosis. Examination revealed: free hydrochloric acid, 0; total acidity, 4; lactic acid, 0. Microscopic examination revealed: leukocytes, yeasts, and sarcinae. The roentgen-ray examination was negative. Bowel movements were variable; he was usually constipated; occasionally he had colic.

Gastroscopy revealed: low stomach; pyloric action normal; mucous membrane in region of antrum elevated, rugged and uneven. On the cardiac sphincter there was a tumor the size of a cherry, pendant into the fornix, and

* Translated by Lynn Rogers, Chicago.

covered with smooth bright red membrane without ulceration. Gastroscopic Diagnosis: Chronic hypertrophic gastritis; small pea-sized tumor of the cardia, myoma or carcinoma.

Although the tumor gave the impression of being benign, gastroscopy was repeated after two and four weeks. Through careful dieting the hypertrophic gastritis was nearly healed, but the tumor was entirely unchanged. On account of its location at the cardia, the diagnosis of myoma, specifically fibromyoma, was made.

CASE 2.—In this case also the tumor was incidental.

M. G., a scrubwoman, aged 45, for three years had had pain in the stomach some time after meals, relieved by eating. There had been vomiting of blood and tarry stools. The condition was diagnosed as being in all probability duodenal ulcer.

Gastroscopy: The whole stomach was well illuminated. Pyloric action was normal. There was no ulcer. The mucosa was very pale. On the anterior wall there was an irregularly bordered area, gray-green and thinned out, the mucous membrane showing no red tint. Somewhat higher but still below the cardia, there was a small half spherical tumor protruding into the lumen and covered with pale mucous membrane. Gastroscopic diagnosis: Anemia; circumscribed atrophic gastritis of the anterior wall and subcardial fibromyoma.

At the second gastroscopic examination the anemia was improved; the other conditions were unchanged.

In both cases I consider the fibroma incidental and believe that its association with unusual gastritic changes is fortuitous and that none of the subjective symptoms have any connection with the tumor.

B. Mucous polyp.—Mucous polyp occurs either solitary or multiple (polyposis ventriculi). We distinguish simple mucous polyp, cystic and papillary adenoma.

CASE 3.—P. H., a day laborer, aged 45, had dysentery during the war. Since then he had had stomach pains unrelated to meals. He had attacks of colic. There were objective signs. A test breakfast revealed free hydrochloric acid, 0; total acidity, 8; lactic acid, 0; absence of pepsin. The microscopic examination was negative. There was no blood in the stools. Diagnosis: Achylia gastrica and gastrogenic diarrhea following dysentery.

Gastroscopy: There were surprising findings in the antrum. A transparent reddish fold contracted and revealed the sphincter of the antrum which after the manner of the pylorus closed tightly with the formation of thick, elevated folds and creases so that the cavity of the antrum became entirely shut off from the gastric cavity. When the folds of the sphincter slowly relaxed they revealed a small irregular tumor between them, on the posterior wall.

The cavity of the antrum was now exposed and a moderately broad expanse of tumor was perceptible on the posterior wall. The normal pylorus became visible beyond.

Diagnosis: Polyp of the posterior wall of the antrum. The polyp could also be demonstrated with the fluoroscope.

In reporting this case I have concluded that the gastric pains are to be explained by the presence of the polyp, which is irritant to the pylorus, producing spasm. This patient was examined twice.

CASE 4.—W. D., a housekeeper, aged 31, thirteen years previously had had an operation for alleged ulcer. On presentation she had pain in the stomach and vomiting. There was no hydrochloric acid or pepsin. Gastroscopy twice

repeated revealed the same condition. The mucous membrane everywhere, and especially in the pyloric region, presented nodular and finger-shaped excrescenses. On the anterior wall there was a hemispherical tumor entirely covered with whitish mucus (most probably an adenomatous polyp). On the posterior wall of the fundus there was a gastro-enterostomy opening, functioning rhythmically and energetically. The pylorus was extant and functioning normally.

Diagnosis: Polyposis ventriculi.

In this case also it is not entirely clear whether the discomfort was caused by the gastro-enterostomy or the polyp. The latter seemed probable, as the gastro-enterostomy functioned normally.

Gastroscopic differential diagnosis between real polyps and the inflammatory growths of gastritis chronica polyposa is not difficult. Real polyps protrude from smooth shiny normal membrane and are themselves covered with smooth orange-colored mucosa. Pseudopolyps of chronic gastritis protrude from a dull, elevated, puffy mucosa and have a bluish translucence.

C. Papilloma.—I have not had an opportunity to observe this rare benign tumor. Through the gastroscope it would be indistinguishable from carcinoma papillosum, also rare. The therapy would therefore necessarily be surgical. The picture presented would resemble the cystoscopic one of papilloma.

MALIGNANT TUMORS

Among metastatic tumors, melanotic sarcomas, easily recognized by their black color, are most frequent. Metastatic carcinomas, which are apt to form multiple nodular and ulcerated metastases, are rare. Sarcomas of various kinds occur in the stomach in addition to the frequent carcinomas.

A. Sarcoma.—The ordinary nodular round-celled sarcomas are not easily distinguishable from similar carcinomas, whereas the diffuse lymphosarcomas present a characteristic picture.

Case 5.—C. N.,[1] a housekeeper, aged 60, had pain in the stomach. She had lost weight and appetite. Examination revealed: no free hydrochloric acid, a total acidity of 5, no rennin, or pepsin, and no lactic acid. Microscopic examination revealed: leukocytes, erythrocytes, bacteria and sarcinae. Roentgen-ray examination revealed stasis in the duodenum.

First gastroscopy: The mucosa of the lesser curvature was elevated; there were areas of submucous hemorrhage which in one place had broken through the mucous membrane. Second gastroscopy: This was performed four months later. The whole membrane was greatly changed, showing everywhere large areas of diffuse hemorrhage. The greater curvature of the fundus presented rigid streaks and bands showing a nodular surface. If it had not been for the greatly advanced changes in the mucosa, the diagnosis might have been carcinoma. The diagnosis was gastritis proliferans of an unusual type. The patient declined operation, and four months later died of perforative peritonitis. Necropsy revealed diffuse lymphosarcoma of the stomach.

1. This case was reported in great detail in Klin. Wchnschr. **42**:2086, 1922.

It is obvious that diagnosis of this case could have been possible only through the gastroscope.

B. Carcinoma.—It is well known that gastric carcinoma is frequent. Surgery is its only chance for cure. The probability of successful radical extirpation is not bad if performed in time. Many patients first show subjective symptoms when the tumor has become inoperable. There is, however, a large percentage of patients in whom a diagnosis could be made much earlier than is the rule at present.

I have formulated this rule: When a person over 35 years of age suffers from gastric disturbances which do not disappear after internal treatment of from four to six weeks or when such a person shows an inexplicable loss of weight, he or she should undergo gastroscopy. I vigorously support this opinion.

Carcinoma presents a different gastroscopic picture in each case. One finds rigid infiltration of the wall, small shallow ulcerations and round cup-shaped tumors which often show crater-like ulcerations. (This is the most common form.) There are also solid, slightly ulcerated tumors and papillomatous tumors.

The picture varies greatly according to location of the tumor. Often parts of tumors, frequently most important parts, remain hidden because of intervening portions of the normal stomach. Ulcer particularly is sometimes hard to discern. At times only a minute part of a large tumor is visible. On account of optical distortion, it is hard at times to judge the exact size of the tumor.

The colors of carcinomas are brilliant in the gastroscope—much brighter than in a postmortem preparation.

In scirrhous infiltration of the stomach wall, the latter takes on an oddly rigid appearance and a grayish white color in sharp contrast to the normal orange hue.

Solid tumors may be covered with apparently normal mucous membrane, protude far into the lumen of the stomach and present only a small ulcer at their summits, or they may expand into a hemispherical form, become brownish purple and throw strong shadows on the pale gastric wall.

In one case there were white nodules probably covered with mucus. It is noteworthy that in the frequent cup-shaped tumors the wall projects, usually dark red, from the much lighter colored normal mucosa. Papillomatous cauliflower tumors are grayish red.

The cancerous ulcer has an irregular eaten-out border. Its borders are usually, not always, elevated, wall-shaped. Its differential diagnosis from benign ulcer is usually easy, but at times difficult and occasionally impossible. Often the pathologic diagnosis can be made only with the microscope.

The base of the ulcer may be vivid yellow or gray-red, like the surrounding mucosa, but much oftener it presents all the appearances of necrosis with marked variations of brown, violet, red, yellow, white and especially green. The green color of necrotic tissues as seen through the gastroscope is particularly characteristic. The mucosa in the region of the tumor occasionally shows small secondary ulcers. Otherwise it gives the picture either of chronic mucous catarrh with petechial injection and stringy and weblike deposits of tenacious mucus; or one sees on the apparently normal mucosa, various large atrophic gray-green islands, the frank picture of an atropic gastritis. Rarely the pallid mucosa is dotted with petechial hemorrhages.

Scirrhous infiltration of the entire stomach wall produces the so-called "canteen stomach," a diminished tube with boardlike walls. As it cannot be inflated, gastroscopy is impossible. The differential diagnosis of certain terminal forms of hypertrophic gastritis can be made only postmortem.

The following is a brief history and description of the gastroscopic findings in twenty-five cases of carcinoma which I have examined. In eleven patients the lesion was at the pylorus, in seven on the lesser curvature, in six on the fundus and in one in the bowel immediately below the opening of a gastro-enterostomy.

CARCINOMA OF THE PYLORUS

Case 6.—A. S., a servant, aged 27, had a "weak stomach." The symptoms had been aggravated during the last three weeks. There were stomach pain, vomiting, extreme cachexia and anemia. Hemoglobin was 19 per cent.; there were 1,300,000 erythrocytes. Emptying of the stomach was delayed. A test breakfast revealed: free hydrochloric acid 10, total acidity 20. Fluoroscopic examination revealed an anatomic obstruction to the emptying of the stomach. Carcinoma was suspected.

Gastroscopy: The mucosa of the fundus was almost white. In the dependant portion there was coffee ground fluid. Before the pylorus could be examined the lamp burned out, and another was not available. Gastroscopic diagnosis: Probably carcinoma. The patient died in eight days. Necropsy revealed a large ulcerated carcinoma of the pylorus. Could gastroscopy have been continued, the large tumor could not have escaped the eye.

Case 7.—J. K., a factory worker, aged 42, had lost weight—four kilograms in four months—and had gastric pain after meals and a poor appetite. Examination showed retarded emptying of the stomach. The gastric juice contained no free hydrochloric acid; it contained lactic acid and blood. The stool contained blood. There was no palpable tumor. Radioscopic examination revealed probably an old ulcer with surrounding hyperplasia. Clinical Diagnosis: suspected carcinoma.

Gastroscopy: The antrum was only partly visible; a broad rigid elevation of the posterior wall intervened obscuring the light. Only a part of the pylorus was visible. It was rigid and without motility. There was no ulceration.

A biopsy was made. Operation revealed carcinoma of the pylorus and greater curvature, which were totally resected.

It is as yet unknown whether complete rigidity of the pylorus means a pathologic process in every case. In conjunction with a rigid elevation of the posterior wall, such a finding established the diagnosis of carcinoma. As a beginner, I did not venture to make it, as I had never seen a tumor through the gastroscope.

In all of the following cases, definite diagnosis was made with the gastroscope.

Case 8.—A. K., aged 64, had lost weight and had pain in the stomach, anemia and palpable tumor. Examination revealed no free hydrochloric acid; lactic acid and blood were present. Radioscopic examination revealed carcinoma of the pylorus.

Gastroscopy: Instead of the pylorus there was a deep crater-like depression; the surface was ulcerated, greenish black and dotted with minute hemorrhages. The ulceration was irregularly bordered by the mucosa of the anterior wall, which formed an elevated edge. Toward the normal anterior wall were mushroom vegetations. On the normal mucosa of the front wall toward the greater curvature was a sharply defined hour-glass shaped ulcer. The posterior wall of the tumor was overlaid with a nodular rigid fold of the posterior stomach wall. Stringy and coffee-ground greenish-brown deposits lay on the neighboring mucosa.

Gastroscopic Diagnosis: Crater-like ulcerated carcinoma of the pylorus involving the anterior and posterior walls of the stomach. At necropsy an ulcerated carcinoma was found involving the whole pyloric canal, extending to the fundus and mesogastrium.

I have described the condition minutely in order to give some conception of the color and plastic details. It would be impossible for the best artist to reproduce the exact coloring.

Case 9.—M. H., a day laborer, aged 62, for three months had lost weight; there had been pain in the stomach, vomiting and anorexia. Emptying of the stomach was greatly delayed. There were free hydrochloric acid, sarcinae and bacteria. Radioscopic examination revealed marked infiltration of the lesser curvature. Clinical diagnosis: Frank carcinoma.

Gastroscopy (with Elsner's instrument): The pylorus was shut out from view by the marked protrusion of the lesser curvature. On the anterior wall of the antrum a reddish, ulcerated mass of tissue projected into the lumen. Gastroscopic diagnosis: Carcinoma of the pyloric region.

Although no necropsy was performed, I cite this case to show that at times only a small part of an unquestionably large tumor is visible.

Case 10.—H. W., a glassblower, had lost weight and had had stomach pain during the past three months. He had had jaundice during the past twenty-eight days. He had large tumor of the liver. The stools were gray. The gastric juice contained no blood or free hydrochloric acid. Radioscopy: The stomach was somewhat enlarged. There was marked peristalsis and displacement to the left. Emptying of the stomach was somewhat delayed. There was duodenal stasis probably caused by some external enlargement or pressure.

Gastroscopy: At the end of the lesser curvature there was a large tumor, with a dark central depression and large gray, greenish and whitish ulcerations. The margin was dark red and wall-like. Gastroscopic Diagnosis: Carcinoma of the pylorus.

Necropsy revealed metastatic carcinoma of the pylorus.

It is noteworthy that in this case gastroscopy proved of more value than radioscopy.

CASE 11.—Q. B., aged 54, during the past year had lost weight and had had pain in the stomach. Radioscopy revealed a defect of the antrum and carcinoma.

First Gastroscopy: Around the funnel of the antrum there was a small abrupt circular tumor wall. The funnel showed red ulceration. Gastroscopic Diagnosis: Circular carcinoma of the pylorus.

The patient refused operation as his condition began to improve.

Second Gastroscopy: The same tumor was present, but the wall was now higher and more rounded. There was much funnel-shaped ulceration.

A biopsy was made. Operation revealed an ulcerated carcinoma of the antrum, the size of a saucer. It was completely resected.

Gastroscopy had therefore clearly shown the enlargement of the tumor notwithstanding the subjective improvement.

CASE 12.—O. N., a porteress, aged 63, two months before had had nausea and had vomited. There was a large palpable tumor in the epigastrium. Radioscopy revealed carcinoma and almost complete stenosis.

Gastroscopy (repeated once): A large elevated, crater-like, ulcerated tumor was found in the pyloric region. The remaining mucosa was pallid. Gastroscopic Diagnosis: Carcinoma of the pylorus. Operation was refused. Necropsy revealed adenocarcinoma of the pylorus.

CASE 13.—M. R., a janitress, aged 56, for the past year had lost weight, had had pain in the stomach and had vomited. There was a tumor in the left umbilical region; there was normal emptying of the stomach. There was no free hydrochloric, or lactic acid or blood in the gastric juice. There was no blood in the stool. Radioscopy revealed a strikingly constant defect in the antrum. Carcinoma was suspected.

Gastroscopy: In the greater curvature there was an elevated tumor with raised margin and dish-shaped ulceration. The ulceration was dirty green-gray. The tumor projected into the antrum and covered the pylorus. The mucosa of the fundus showed gray-green atrophic areas traversed by fine vessels. Gastroscopic Diagnosis: Large extensively ulcerated carcinoma of the antrum and greater curvature. Biopsy was performed. Operation confirmed the gastroscopic findings. A large tumor was completely resected.

CASE 14.—B. G., a cook, aged 47, had had pain in the stomach for two years. In spite of radioscopic examination, her physician made a diagnosis of gastritis. Finally there was coffee-ground vomiting. There was a palpable tumor. Radioscopic diagnosis was carcinoma of the pylorus.

Gastroscopy: On the pyloric portion of the anterior wall there was a rough nodular ulcerated tumor covered with yellow secretion. The mucosa of the lesser curvature was markedly indented. Gastroscopic Diagnosis: Carcinoma of the pylorus with extension to the anterior wall and lesser curvature.

Necropsy revealed medullary carcinoma of the pyloric region with extension to the lesser curvature and anterior stomach wall.

CASE 15.—J. S., a machinist, aged 60, for the past five months had been treated for gastric catarrh. There had been loss of weight and vomiting of blood. Emptying of the stomach was delayed. There was no free hydrochloric acid, lactic acid was present. Microscopic examination revealed leukocytes, fat droplets, sarcinae, yeasts and lactic acid bacilli. There was an enormous tumor.

Gastrosopy: The fundus contained blackish fluid. In the antrum behind a rigid fold were granulation-like reddish ulcerated growths. There was a blackish brown coating. Gastroscopic Diagnosis: Carcinoma of the pyloric region.

Necropsy revealed a sharply defined large necrotic, disintegrating carcinomatous ulcer of the pylorus.

CASE 16.—P. R., a day laborer, aged 57, had lost weight and had had pain in the stomach, pyloric stenosis and blood in the stool. Gastroscopy: There was a rather long tumor of the greater curvature of the antrum with raised margin, extensively ulcerated. Across the ulcerated area stretched many tough threads of mucus.

Biopsy was performed. Operation revealed a carcinoma of the greater curvature at the pylorus, which was resected.

CARCINOMA OF THE LESSER CURVATURE

It is perhaps no accident that two "early" diagnoses proved to be carcinoma of the lesser curvature. By "early" diagnosis is meant a diagnosis made at a time at which the unquestionable recognition of carcinoma is not yet possible by methods other than gastroscopy and while the tumor is still operable.

CASE 17.—A. R., a watchman, aged 60, had no gastric symptoms. There were merely weakness and loss of weight. Three years before he had had tuberculosis of the right shoulder-joint. Five years before he had had pulmonary hemorrhage. He now had extensive indurated tuberculosis of the right upper lobe. He had marked anemia (hemoglogin, 38 per cent.). The stools showed occult blood. Tuberculosis of the bowel was first suspected. There was no free hydrochloric acid. Radioscopy revealed a flabby stomach sagging toward the colon and diverticular outpouching of the greater curvature (malformation). The consulting surgeon refused surgical intervention because of doubtful diagnosis and the serious pulmonic lesion.

First Gastroscopy: There was a rigid spastic fold protruding from the anterior wall.

Second Gastroscopy: The pylorus was clearly focused. There was active motility, type 2.

As the pylorus contracted, a red half-spherical prominence appeared on the lesser curvature of the antrum cavity, half covering the latter during contraction, and having at its apex a small yellow point. When the pylorus relaxed, it disappeared behind the gastric curvature. This was observed for some time.

A biopsy was made. Operation was performed because of the foregoing findings. There was carcinoma (microscopic: adenocarcinoma) of the lesser curvature not extending to the sphincter. A shallow ulcer with an elevated margin was resected.

The medical practitioner could without doubt often obtain equally satisfactory results by resorting to early gastroscopy in the case of gastric disease or of old people who are anemic and losing weight.

CASE 18.—A. N., a clerk, aged 54, had gastric pains after meals. He had lost weight and had vomited during five months. There was some mucus in the stomach after a test breakfast. There was no free hydrochloric acid and no blood in the stool. No tumor mass was present. Radioscopy revealed a rather long fish-hook stomach and marked peristalsis. Emptying of the stomach was somewhat retarded. There was no evidence of tumor. Duodenal stricture was suspected.

First Gastroscopy: The stomach contained large masses of thick glairy mucus, mixed with blood which obscured the view of the lower portion of the organ.

Second Gastroscopy: Excellent view was obtained. The pylorus contracted normally and completely (Type 1), expelling fluid. At the angle was

the ropelike sphincter muscle of the antrum. Immediately above on the lesser curvature was an ulceration. Its border toward the posterior wall was somewhat irregular. The intact mucosa joined it without elevation and was a vivid red. The anterior border showed two nodules which partly masked the yellow base. Gastroscopic Diagnosis: Ulcer of the lesser curvature, probably carcinoma.

A biopsy was made. Operation revealed a tumor between the gastric angle and the cardia, which was resected. The ulcer measured 2.7 by 3.7 cm. Microscopic examination revealed that it was partly adenosarcoma and partly solid carcinoma.

CASE 19.—A. B., a worker by the day, aged 46, had lost weight and had pain in the stomach after meals. There was no free hydrochloric acid or occult blood in the stool. Gastroscopy: At the angle of the lesser curvature there was an ulcerated tumor with raised margin. Gastroscopic Diagnosis: Carcinoma of the lesser curvature.

A biopsy was made. Operation confirmed the diagnosis.

CASE 20.—J. R., a farmhand, aged 38, had lost weight; he had poor appetite and pain in the back. There was a palpable tumor of the stomach and blood in the stool. The condition was frank carcinoma.

Gastroscopy: The anterior wall and lesser curvature protruded so far and so rigidly that they pressed against the optic and were not moved away by inflation. On a fold of the anterior wall a flat ulceration was surrounded by blood infiltration. Gastroscopic diagnosis was carcinoma of the anterior wall and lesser curvature.

In the following case the ulcer could not be brought to view. Only the neoplastic infiltration of the mucosa furnished the diagnosis.

CASE 22.—G. N., a helper, aged 57, had lost weight and had had severe gastric pain, after eating, of four months' duration. There was a palpable tumor. He had pyloric stenosis. Radioscopy yielded nothing definite, but clinically there was no doubt that the condition was carcinoma.

Gastroscopy: There was a small dark brown mass in the fundus. There was a marked tumor prominence of the lesser curvature so large that it obstructed any view of the pyloric region. From the anterior to the posterior wall stretched a glistening mucous band partly infiltrated with blood. In the anterior wall of the lesser curvature, there was a fold bordered area, depressed and less glistening, with a peculiar gray and rigid appearance. Gastroscopic Diagnosis: Scirrhous carcinoma of the lesser curvature. Biopsy revealed carcinoma of the lesser curvature, well advanced. It could not be resected because of metastases to the glands. Gastro-enteroanastomosis was performed.

Necropsy. The same findings.

In the following case the gastroscopic picture was more distinctive than the macroscopic picture at necropsy. The final diagnosis was made by the microscope.

CASE 23.—K. S., a typesetter, aged 48, had lost weight and had gastric pain. Radioscopy revealed that there was probably carcinoma of the pylorus, and carcinomatous ascites. Gastroscopy: High up on the lesser curvature there was a large deeply fissured tumor-like area. It was dirty gray-green or gray-yellow, the margin being somewhat raised. Further entrance by the gastroscope was impossible. Gastroscopic Diagnosis: Carcinoma of the lesser curvature. At necropsy it was found that the mucosa was macroscopically unchanged. A tumor appeared to arise in the tail of the pancreas and infiltrate the stomach wall. Microscopic examination revealed adenocarcinoma of the stomach. The mucosa of the lesser curvature was extensively necrotic.

CARCINOMA OF THE FUNDUS

Carcinoma of the fundus occasionally renders the introduction of the instrument exceedingly difficult, especially so the higher up it is located. Gastroscopy of carcinoma of the cardia is obviously not feasible. Esophagoscopy is the method to be used.

CASE 24.—F. B., locomotive engineer, aged 58, had lost weight and appetite and had gastric pain. Examination revealed no free hydrochloric acid. There was much blood in the stool. Radioscopy revealed a tumor-like bulging on the anterior wall. Between this and the posterior wall there was a small fissure on the greater curvature discharging blackish green fluid. Below the conical bulging of the front wall there was a nodular red excresence. Gastroscopic Diagnosis: Carcinoma of the posterior wall and greater curvature of the fundus. A biopsy was performed. Operation revealed carcinoma at the site specified. The tumor was resected.

CASE 25.—M. D., a coachman, aged 60, had lost weight and had gastric pain. There was no free hydrochloric acid, or blood in the stool. Radioscopy revealed a probable tumor.

Gastroscopy: It was not possible to obtain a clear view of the anterior wall of the lesser curvature of the fundus because of the close proximity of the instrument to this surface. By moving the prism downward to the right with the patient in the left-sided position, the extremely pale mucosa was seen to be injected with small hemorrhages. To the left was a large prominent brownish violet tumor. Gastroscopic Diagnosis: Carcinoma of the anterior wall and greater curvature of the fundus. Necropsy confirmed the diagnosis.

The following case shows that the gastroscopic finding may be of importance as an indication for treatment.

CASE 26.—Bertha A., a cook, aged 27, had had hypogastric pain for six weeks. Five months before bilateral ovarian carcinomas had been removed. A few weeks later there were symptoms of ileus. Now there was a recurrence in the pelvis, compressing the rectum. It was the intention to give deep roentgen-ray treatment, but radioscopy of the stomach and bowel showed, besides dilatation of numerous intestinal loops, a defect of the greater curvature. Irradiation should be used only when the stomach is not involved.

Gastroscopy: The anterior wall, lesser curvature and pyloric region were rigidly infiltrated. The antrum presented a rigid trough. The pylorus was not patent. On the greater curvature of the fundus is a grayish-red ulceration with a high wall-like margin. Gastroscopic Diagnosis: Carcinomatous ulcer of the greater curvature; probable extensive infiltration of the stomach wall.

It follows that the ovarian carcinomas were metastases from the primary gastric cancer. The treatment was purely symptomatic, irradiation being discarded. Necropsy fully confirmed the diagnosis.

CASE 27.—C. K., a mason, aged 51, had profuse hematemesis without loss of weight or definite symptoms. Diagnosis: Probably round ulcer. The stools were free from blood after four weeks. Three weeks later there was vomiting and no free hydrochloric acid.

Gastroscopy: The anterior wall was difficult to focus. The posterior wall was very well focused. Just below the cardia there was the elevated margin of a fissured yellowish white ulcer of the greater curvature. The wall presented rough nodules and depressions. Gastroscopic Diagnosis: Carcinoma of the corpus. Radioscopy confirmed the diagnosis. Necropsy revealed carcinoma of the corpus, perforating into the liver.

The following is the only finely nodular cauliflower carcinoma in my series.

CASE 28.—I. O., a man, retired, aged 68, suffered from loss of weight, pain, vomiting and a palpable tumor.

Gastroscopy: On the greater curvature of the corpus there was a projecting, finely nodular cauliflower growth. There was bloody, fluid mucus. Gastroscopic Diagnosis; carcinoma of the corpus.

The next case presents a maneuver in gastroscopic technic which the beginner should never imitate.

CASE 29.—J. K., a day laborer, aged 53, for the past six months had had gastric pain immediately after meals and he vomited. There was no free hydrochloric acid or blood in the stool. However, the diagnosis of ulcer with hour-glass stomach was made in two roentgen-ray institutes. Clinically, however, the suspicion of carcinoma of the cardia remained.

Gastroscopy: It was not possible to introduce the gastroscope as the rigid portion met an impassible obstruction at the cardia. Therefore the obturator tube was withdrawn and the optic tube carefully pushed in, and although the mark was still somewhat above the teeth, it was possible to obtain a view. The cardia arched forward, sickle-shaped. Below was a crater-like sloping mucosa. On the floor of the crater was an irregular ulcer covered with ragged dirty gray-yellow membrane. Below was the cavity of the stomach. From it dark Burgundy red fluid flowed over the ulcer. Gastroscopic Diagnosis: Carcinoma of the greater curvature of the fornix.

A biopsy was made. Operation confirmed the diagnosis. The cancer infiltrated the colon. The colon and stomach were resected. It was necessary to divide the lesser curvature immediately below the cardia.

CARCINOMA BENEATH A GASTRO-ENTEROSTOMY OPENING

In this case, gastroscopy accomplished a unique and brilliant diagnosis, an early diagnosis which has already been reported. It will be mentioned only briefly here.

CASE 30.—E. B., a shoemaker's wife, aged 44, had had an operation on the stomach eleven years before. She had lost weight during the last two months and was anemic. Radioscopy revealed a functioning gastro-enterostomy. Otherwise the examination was negative. Clinical Diagnosis: Suspicion of ulcer.

Gastroscopy: In the deepest portion of the fundus, there was a collection of ragged gray-yellow masses floating in fluid. On the greater curvature, there was an oval opening which opened and closed rhythmically. On closing, it discharged the same shreddy material seen in the fundus. On its upper margin, there were two small yellow-coated ulcers. In the pyloric region there was a binodular polypoid excrescence. The pylorus was not visible. Gastroscopic Diagnosis: Malignant tumor immediately beneath a gastro-enterostomy —peptic ulcer.

A biopsy was made. Just previous to the operation it was learned that the pylorus had been resected eleven years before because of carcinoma. The old microscopic preparation confirmed it. There proved to be a carcinomatous recurrence in the colon beneath the gastro-enterostomy opening which it was possible to resect, together with the ulcers and the stump of the pylorus.

In this connection it may be mentioned that another case came to operation in which the radioscopic diagnosis of carcinoma was made while nothing was found with the gastroscope. At operation the stomach revealed no pathologic change.

SUMMARY

Four benign and twenty-six malignant gastric tumors were demonstrated by gastroscopy. Of the four benign tumors two were fibromyomas, one solitary mucous polyp and one polyposis.

Of the twenty-six malignant tumors, one was diffuse lymphosarcoma and twenty-five carcinoma. Ten were confirmed by biopsy, eleven by necropsy, two by biopsy and necropsy. The findings were always in full accord. In three cases, early diagnosis of carcinoma was possible.

Through systematic employment of this modification of the gastroscope, I hope that early diagnosis of carcinoma will be definitely advanced.